

RECEIVED PTO 15 FEB 2005

NOVEL PYRAZOLOPYRIDINE DERIVATIVES AS PHARMACEUTICAL AGENTS

The invention relates to new pyrazolopyridine derivative compounds and their use as pharmaceutical agents, in particular their use as TGF-beta signal transduction inhibitors.

BACKGROUND OF THE INVENTION

The transforming growth factor-beta (TGF-Beta)("TGF- β ") polypeptides influence growth, differentiation, and gene expression in many cell types. The first polypeptide of this family that was characterized, TGF- β 1, has two identical 112 amino acid subunits that are covalently linked. TGF- β 1 is a highly conserved protein with only a single amino acid difference distinguishing humans from mice. There are two other members of the TGF- β gene family that are expressed in mammals. TGF- β 2 is 71% homologous to TGF- β 1 (de Martin, et al. (1987) EMBO J. 6:3673-3677), whereas TGF- β 3 is 80% homologous to TGF- β 1 (Derynck, et al. (1988) EMBO J 7:3737-3743). The structural characteristics of TGF- β 1 as determined by nuclear magnetic resonance (Archer, et al. (1993) Biochemistry 32:1164-1171) agree with the crystal structure of TGF- β 2 (Daopin, et al. (1992) Science 257:369-374; Schlunegger and Grutter (1992) Nature 358:430-434).

There are at least three different extracellular TGF- β receptors, Type I, II and III that are involved in the biological functions of TGF- β 1, - β 2 and - β 3 (For reviews, see Derynck (1994) TIBS 19:548-553 and Massague (1990) Ann. Rev. Cell Biol. 6:597-641).

The Type I and Type II receptors are transmembrane serine/threonine kinases which in the presence of TGF- β form a heteromeric signaling complex (Wrana, et al (1992) Cell 71: 1003-1014). The mechanism of activation of the heteromeric signaling complex at the cell surface has been elucidated (Wrana, et al. (1994) Nature 370: 341-347). TGF- β first binds the type II receptor which is a constitutively active transmembrane serine/threonine kinase. The type I receptor is subsequently recruited into the complex, phosphorylated at the GS domain and activated to phosphorylate downstream signaling components (e.g. Smad proteins) to initiate the intracellular signaling cascade. A constitutively active type I receptor (T204D mutant) has been shown to effectively

transduce TGF- β responses, thus bypassing the requirement for TGF- β and the type II receptor (Wieser, et al. (1995) EMBO J 14: 2199-2208). Although no signaling function has been discovered for the type III receptor, it does increase TGF- β 2's affinity for the type II receptor making it essentially equipotent with TGF- β 1 and TGF- β 3 (Lopez-
5 Casillas, et al. (1993) Cell 73: 1435-1444).

Vascular endothelial cells lack the Type III receptor. Instead endothelial cells express a structurally related protein called endoglin (Cheifetz, et al. (1992) J. Biol. Chem. 267:19027-19030), which only binds TGF- β 1 and TGF- β 3 with high affinity. Thus, the relative potency of the TGF- β 's reflect the type of receptors expressed in a cell
10 and organ system. In addition to the regulation of the components in the multi-factorial signaling pathway, the distribution of the synthesis of TGF- β polypeptides also affects physiological function. The distribution of TGF- β 2 and TGF- β 3 is more limited (Derynck, et al. (1988) EMBO J 7:3737-3743) than TGF- β 1, e.g., TGF- β 3 is limited to tissues of mesenchymal origin, whereas TGF- β 1 is present in both tissues of
15 mesenchymal and epithelial origin.

TGF- β 1 is a multifunctional cytokine critical for tissue repair. High concentrations of TGF- β 1 are delivered to the site of injury by platelet granules (Assoian and Sporn (1986) J. Cell Biol. 102:1217-1223). TGF- β 1 initiates a series of events that promote healing including chemotaxis of cells such as leukocytes, monocytes and
20 fibroblasts, and regulation of growth factors and cytokines involved in angiogenesis, cell division associated with tissue repair and inflammatory responses. TGF- β 1 also stimulates the synthesis of extracellular matrix components (Roberts, et al. (1986) Proc. Natl. Acad. Sci. USA 83:4167-4171; Sporn, et al. (1983) Science 219:1329-1330; Massague (1987) Cell 49:437-438) and most importantly for understanding the
25 pathophysiology of TGF- β 1, TGF- β 1 autoregulates its own synthesis (Kim, et al. (1989) J. Biol. Chem. 264:7041-7045).

A number of diseases have been associated with TGF- β 1 over production. Fibrotic diseases associated with TGF- β 1 overproduction can be divided into chronic conditions such as fibrosis of the kidney, lung and liver and more acute conditions such as
30 dermal scarring and restenosis. Synthesis and secretion of TGF- β 1 by tumor cells can also lead to immune suppression such as seen in patients with aggressive brain or breast

tumors (Arteaga, et al. (1993) J. Clin. Invest. 92:2569-2576). The course of Leishmanial infection in mice is drastically altered by TGF- β 1 (Barral-Netto, et al. (1992) Science 257:545-547). TGF- β 1 exacerbated the disease, whereas TGF- β 1 antibodies halted the progression of the disease in genetically susceptible mice. Genetically resistant mice
5 became susceptible to Leishmanial infection upon administration of TGF- β 1.

The profound effects of TGF- β 1 on extracellular matrix deposition have been reviewed (Rocco and Ziyadeh (1991) in Contemporary Issues in Nephrology v.23, Hormones, autocoids and the kidney. ed. Jay Stein, Churchill Livingston, New York pp.391-410; Roberts, et al. (1988) Rec. Prog. Hormone Res. 44:157-197) and include the
10 stimulation of the synthesis and the inhibition of degradation of extracellular matrix components. Since the structure and filtration properties of the glomerulus are largely determined by the extracellular matrix composition of the mesangium and glomerular membrane, it is not surprising that TGF- β 1 has profound effects on the kidney. The Accumulation of Mesangial Matrix in Proliferate Glomerulonephritis (Border, et al.
15 (1990) Kidney Int. 37:689-695) and diabetic nephropathy (Mauer, et al. (1984) J. Clin. Invest. 74:1143-1155) are clear and dominant pathological features of the diseases. TGF- β 1 levels are elevated in human diabetic glomerulosclerosis (advanced neuropathy) (Yamamoto, et al. (1993) Proc. Natl. Acad. Sci. 90:1814-1818). TGF- β 1 is an important mediator in the genesis of renal fibrosis in a number of animal models (Phan, et al. (1990)
20 Kidney Int. 37:426; Okuda, et al. (1990) J. Clin. Invest. 86:453). Suppression of experimentally induced glomerulonephritis in rats has been demonstrated by antiserum against TGF- β 1 (Border, et al. (1990) Nature 346:371) and by an extracellular matrix protein, decorin, which can bind TGF- β 1 (Border, et al. (1992) Nature 360:361-363).

Too much TGF- β 1 leads to dermal scar-tissue formation. Neutralizing TGF- β 1
25 antibodies injected into the margins of healing wounds in rats have been shown to inhibit scarring without interfering with the rate of wound healing or the tensile strength of the wound (Shah, et al. (1992) Lancet 339:213-214). At the same time there was reduced angiogenesis, reduced number of macrophages and monocytes in the wound, and a reduced amount of disorganized collagen fiber deposition in the scar tissue.

30 TGF- β 1 may be a factor in the progressive thickening of the arterial wall which results from the proliferation of smooth muscle cells and deposition of

extracellular matrix in the artery after balloon angioplasty. The diameter of the restenosed artery may be reduced 90% by this thickening, and since most of the reduction in diameter is due to extracellular matrix rather than smooth muscle cell bodies, it may be possible to open these vessels to 50% simply by reducing extensive
5 extracellular matrix deposition. In uninjured pig arteries transfected in vivo with a TGF- β 1 gene, TGF- β 1 gene expression was associated with both extracellular matrix synthesis and hyperplasia (Nabel, et al. (1993) Proc. Natl. Acad. Sci. USA 90:10759-10763). The TGF- β 1 induced hyperplasia was not as extensive as that induced with PDGF-BB, but the extracellular matrix was more extensive with TGF- β 1
10 transfectants. No extracellular matrix deposition was associated with FGF-1 (a secreted form of FGF) induced hyperplasia in this gene transfer pig model (Nabel (1993) Nature 362:844-846).

There are several types of cancer where TGF- β 1 produced by the tumor may be deleterious. MATLyLu rat cancer cells (Steiner and Barrack (1992) Mol. Endocrinol
15 6:15-25) and MCF-7 human breast cancer cells (Arteaga, et al. (1993) Cell Growth and Differ. 4:193-201) became more tumorigenic and metastatic after transfection with a vector expressing the mouse TGF- β 1. In breast cancer, poor prognosis is associated with elevated TGF- β (Dickson, et al. (1987) Proc. Natl. Acad. Sci. USA 84:837-841; Kasid, et al. (1987) Cancer Res. 47:5733-5738; Daly, et al. (1990) J. Cell Biochem. 43:199-211;
20 Barrett-Lee, et al. (1990) Br. J Cancer 61:612-617; King, et al. (1989) J. Steroid Biochem. 34:133-138; Welch, et al. (1990) Proc. Natl. Acad. Sci. USA 87:7678-7682; Walker, et al. (1992) Eur. J. Cancer 238:641-644) and induction of TGF- β 1 by tamoxifen treatment (Butta, et al. (1992) Cancer Res. 52:4261-4264) has been associated with failure of tamoxifen treatment for breast cancer (Thompson, et al. (1991) Br. J. Cancer 63:609-
25 614). Anti TGF- β 1 antibodies inhibit the growth of MDA-231 human breast cancer cells in athymic mice (Arteaga, et al. (1993) J. Clin. Invest. 92:2569-2576), a treatment which is correlated with an increase in spleen natural killer cell activity. CHO cells transfected with latent TGF- β 1 also showed decreased NK activity and increased tumor growth in nude mice (Wallick, et al. (1990) J. Exp. Med. 172:1777-1784). Thus, TGF- β secreted by
30 breast tumors may cause an endocrine immune suppression. High plasma concentrations of TGF- β 1 have been shown to indicate poor prognosis for advanced breast cancer

patients (Anscher, et al. (1993) N. Engl. J. Med. 328:1592-1598). Patients with high circulating TGF- β before high dose chemotherapy and autologous bone marrow transplantation are at high risk for hepatic veno-occlusive disease (15-50% of all patients with a mortality rate up to 50%) and idiopathic interstitial pneumonitis (40-60% of all patients). The implication of these findings is 1) that elevated plasma levels of TGF- β 1 can be used to identify at risk patients and 2) that reduction of TGF- β 1 could decrease the morbidity and mortality of these common treatments for breast cancer patients.

Many malignant cells secrete transforming growth factor- β (TGF- β), a potent immunosuppressant, suggesting that TGF- β production may represent a significant tumor escape mechanism from host immunosurveillance. Establishment of a leukocyte sub-population with disrupted TGF- β signaling in the tumor-bearing host offers a potential means for immunotherapy of cancer. Down regulation of TGF- β secretion in tumor cells results in restoration of immunogenicity in the host, while T-cell insensitivity to TGF- β results in accelerated differentiation and autoimmunity, elements of which may be required in order to combat self-antigen-expressing tumors in a tolerized host. The rationale, approaches, and potential pitfalls of this strategy will be discussed.

Cancer: During the earliest stages of carcinogenesis, TGF- β 1 can act as a potent tumor suppressor and may mediate the actions of some chemopreventive agents. However, at some point during the development and progression of malignant neoplasms, tumor cells appear to escape from TGF- β -dependent growth inhibition in parallel with the appearance of bioactive TGF- β in the microenvironment. Thus, the production of TGF- β 1 by malignant cells in primary tumors appears to increase with advancing stages of tumor progression. Studies in many of the major epithelial cancers suggest that the increased production of TGF- β by human cancers occurs as a relatively late event during tumor progression. Further, this tumor-associated TGF- β provides the tumor cells with a selective advantage and promotes tumor progression. The effects of TGF- β on cell/cell and cell/stroma interactions result in a greater propensity for invasion and metastasis. Tumor-associated TGF- β may allow tumor cells to escape from immune surveillance since it is a potent inhibitor of the clonal expansion of activated lymphocytes. TGF- β has also been shown to inhibit the production of angiostatin. Cancer therapeutic modalities such as radiation therapy and chemotherapy induce the production of activated TGF- β in

the tumor, thereby selecting outgrowth of malignant cells that are resistant to TGF- β growth inhibitory effects. Thus, these anticancer treatments increase the risk and hasten the development of tumors with enhanced growth and invasiveness. In this situation, agents targeting TGF- β 1 itself might be a very effective therapeutic strategy. The
5 resistance of tumor cells to TGF- β has been shown to negate much of the cytotoxic effects of radiation therapy and chemotherapy and the treatment-dependent activation of TGF- β in the stroma may even be detrimental as it can make the microenvironment more conducive to tumor progression and contributes to tissue damage leading to fibrosis. The development of a TGF- β 1 neutralizing agent is likely to benefit the treatment of
10 progressed cancer alone and in combination with other therapies.

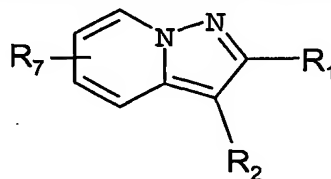
Epithelial and hematopoietic cells have a high turnover and their progenitor cells divide continuously, making them prime targets for genetic and epigenetic changes that lead to cell transformation and tumorigenesis. The consequent changes in cell behavior and responsiveness result not only from genetic alterations such as activation of
15 oncogenes or inactivation of tumor suppressor genes, but also from altered production of, or responsiveness to, stimulatory or inhibitory growth and differentiation factors.

Among these, transforming growth factor beta (TGF-beta) and its signaling effectors act as key determinantsof carcinoma cell behavior. The autocrine and paracrine effects of TGF-beta on tumor cells and the tumor micro-environment exert both positive
20 and negative influences on cancer development.

Accordingly, the TGF-beta signaling pathway has been considered as both a tumor suppressor pathway and a promoter of tumor progression and invasion. Derynck, R., Akhurst, R. & Balmain, A., TGF-beta signaling in tumor suppression and cancer progression, Nature Genetics, Vol. 29, October, 2001.

SUMMARY OF THE INVENTION

The invention herein disclosed is directed to compounds of the structure:



Formula I

Wherein:

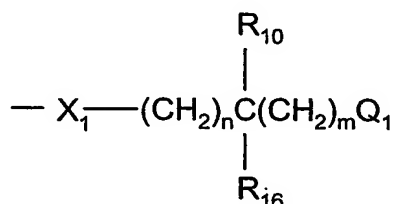
R1 is unsubstituted or substituted pyridine; unsubstituted or substituted furyl; or unsubstituted or substituted thiophenyl; wherein the substitution may be one or more of the following: (C1-C6)alkyl, (C2-C6)alkenyl, (C1-C6)alkoxy, (C1-C6)alkylthio, trifluoromethyl, halo, N-morpholino, phenylthio;

R2 is unsubstituted or substituted quinoline; unsubstituted or substituted phenyl; unsubstituted or substituted naphthalene; unsubstituted or substituted pyridine; unsubstituted or substituted pyrimidine; unsubstituted or substituted quinazoline; unsubstituted or substituted cinnoline; unsubstituted or substituted indole; unsubstituted or substituted; unsubstituted or substituted benzofuran; unsubstituted or substituted dihydrobenzofuran; unsubstituted or substituted dihydrobenzo[1,4]dioxane; unsubstituted or substituted benzodioxolane; unsubstituted or substituted benzothiophene; unsubstituted or substituted 2-aminobenzimidazole; unsubstituted or substituted imidazo[1,2-a]pyridine; wherein the substitution may independently be one or more of the following: hydrogen, (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6) alkylhalide, (C1-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C1-C6)alkoxycarbonyl, N-(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, aminoxy, N-(C1-C6)alkyl aminoxy, N,N-di-[(C1-C6)alkyl]aminoxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N-(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N-(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N-(C1-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, N-(C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N-(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, ethylene, phenyl,

-8-

thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yl-oxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl), N, N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,

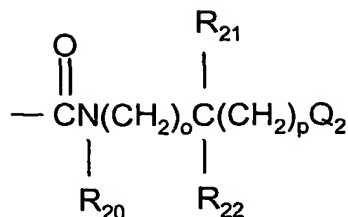
or a group of the formula:



wherein: X_1 is O, N, S, SO_2 , NR_{13} , C(O), or bond; Q_1 is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), C(O) Q_5 , or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; Q_1 is OR_{11} , $\text{NR}_{11}\text{R}_{12}$, halo, N-morpholino, N-piperazino- $\text{N}'\text{R}_{13}$, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), SO_2R_{14} , SOR_{14} , $\text{NHSO}_2\text{R}_{15}$, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoxazolidino, N-pyrrolidinonyl, N(N'-methylbenzimidazolino), N,N-di(C1-C4)alkylamino(C1-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; Q_5 is hydroxy, methoxy, amino, diethylamino, dimethylamino; R_{10} is hydrogen, halo, (C1-C6)alkyl; R_{11} and R_{12} are independently hydrogen, (C1-C6)alkyl, (C1-C6)alkoxy, arylalkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkylmethyl, 4-(N-methylpiperidinyl), pyridyl, or R_{11} and R_{10} can be taken together to form a 4, 5, 6, or 7 membered ring, or R_{11} and R_{12} can be taken together to form a 3, 4, 5, 6, or 7 membered ring; R_{13} is hydrogen, (C1-C6)alkyl, 2-methoxyphenyl, 2-pyridimidinyl; R_{14} is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; R_{15} is (C1-C6)alkyl, N-methyl-4-imidazolyl; R_{16} is hydrogen, halo, arylalkyl, aryl,

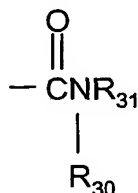
-9-

or a group of the formula:



- wherein: Q₂ is hydrogen, 4-imidazolyl, or C(O)NR₂₄R₂₅ when o and p are independently 0-2; Q₂ is OR₂₃, NR₂₄R₂₅, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; R₂₀ is hydrogen, or (C1-C6)alkyl; R₂₁ is hydrogen, (C1-C6)alkyl, or R₂₁ and R₂₀ can be taken together to form a 4, 5, 6, or 7 membered ring; R₂₂ is hydrogen, (C1-C6)alkyl, arylalkyl, aryl, or R₂₁ and R₂₂ can be taken together to be a 3, 4, 5, 6, 7 membered ring; R₂₃ is hydrogen or (C1-C6)alkyl; R₂₄ is hydrogen, (C1-C6)alkyl, or R₂₄ and R₂₅ can be taken together to form a 3, 4, 5, 6, or 7 membered ring, or R₂₄ and R₂₀ can be taken together to form a 6 or 7 membered ring; R₂₅ is hydrogen, (C1-C6)alkyl, or acetyl,

or a group of the formula:



- wherein: R₃₀ is hydrogen, or (C1-C6)alkyl; R₃₁ is hydrogen, (C1-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy,

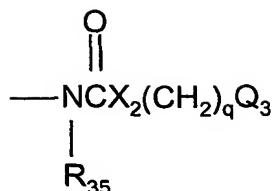
or a group of the formula:



- wherein: R₃₂ and R₃₃ are each independently hydrogen, (C1-C6)alkyl, acetyl, (C1-C4)alkylsulphonyl, or R₃₂ and R₃₃ can be taken together to form a 4, 5, 6, or 7 membered ring,

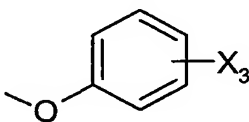
-10-

or a group of the formula:



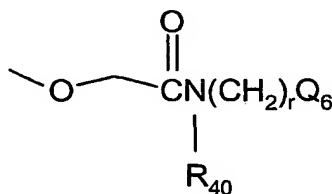
wherein: X_2 is CH_2 , O, or N; q is 2-3 except when Q_3 is a bond, q is 0-3; Q_3 is $\text{NR}_{36}\text{R}_{37}$, or OR_{38} , and R_{35} is hydrogen, or R_{35} and Q_3 can be taken together to form a 5 membered ring; R_{36} , R_{37} , and R_{38} are each independently hydrogen, or (C1-C6)alkyl,

or a group of the formula:



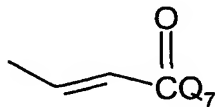
wherein: X_3 is cyano, carboxamide, N,N-dimethylcarboxamide, N,N-dimethylthiocarboxamide, N,N-dimethylaminomethyl, 4-methylpiperazin-1-yl-methyl or carboxylate,

or a group of the formula:



wherein: Q_6 is $\text{NR}_{41}\text{R}_{42}$; r is 2-3; R_{40} is hydrogen, or (C1-C6)alkyl; R_{41} and R_{42} are hydrogen, (C1-C6)alkyl, or R_{41} and R_{40} can be taken together to form a 6 or 7 membered ring,

or a group of the formula:



wherein: Q_7 is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

and wherein R₇ is hydrogen; benzyl; aryl; C₁-C₄ alkyls; halogen; -CO₂(C₁-C₄ alkyl); -CONR₆R₆; -C₁-C₄ alcohol; -SO₂(C₁-C₄ alkyl); -COR₈;

wherein R₆ is (C₁-C₄alkyl)R₉; R₈ is (C₁-C₄alkyl) or (C₂-C₄alkenyl); and R₉ is NR₃R₄, wherein R₃ and R₄ are each independently (C₁-C₄alkyl);

5 and the pharmaceutically acceptable salts, esters and prodrugs thereof.

The compounds are useful for the treatment of cancer and other disease states influenced by TGF beta, such as fibrosis, atherosclerosis, Alzheimer's disease, wound healing, HIV infection and restenosis, and inflammation, including, but not limited to, for example, arthritis, inflammatory bowel disease, Crohn's disease, irritable bowel
10 syndrome, ulcerative colitis, etc., by inhibiting TGF-β in a patient in need thereof by administering said compound(s) to said patient.

DETAILED DESCRIPTION OF THE INVENTION

15 The general chemical terms used herein have their usual meanings. For example, as used herein, the term "C₁-C₄ alkyl", alone or in combination, denotes a straight-chain or branched-chain C₁-C₄ alkyl group consisting of carbon and hydrogen atoms, examples of which are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, and the like. The term "geminal dimethyl" represents two methyl groups attached at the same
20 substitution position. The term "C₃-C₆ cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The term "spiro-fused C₃-C₆ cycloalkyl" refers to a C₃-C₆ cycloalkyl group as defined above bonded to a carbon atom through a spiro linkage.

The term "C₁-C₄ alkoxy", alone or in combination, denotes an alkyl group as defined earlier, which is attached via an oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, and the like. The term "C₁-C₄
25 alkylthio", alone or in combination, denotes an alkyl group as defined earlier and is attached via a sulfur atom, and includes methylthio, ethylthio, isobutylthio, and the like.

As used herein, the term "halo" or "halogen" represents fluorine, chlorine, bromine, or iodine. The term "hydroxy," alone or in combination, represents an -OH
30 moiety. The term "carboxy" or "carboxyl" refers to a carboxylic acid. The term "carboxamide" refers to a carbonyl substituted with an -NH₂ moiety. The term "oxo" refers to a carbonyl group.

As used herein, the term "heteroaryl" means an aryl moiety, which contains 1-5 heteroatoms selected from O, S, and N. Examples of heteroaryl groups include pyrrolyl, pyrazolyl, pyranyl, thiopyranyl, furanyl, imidazolyl, pyridyl, thiazolyl, triazinyl, phthalimidyl, indolyl, purinyl, and benzothiazolyl.

5 As used herein, the term "aryl" represents a substituted or unsubstituted phenyl or naphthyl. Aryl may be optionally substituted with one or more groups independently selected from hydroxy, carboxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, halogen, carboxamide, trifluoromethyl, hydroxymethyl, and hydroxy(C₁-C₄)alkyl.

10 The term "C₃-C₈ cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "optionally substituted C₃-C₈ cycloalkyl" refers to a C₃-C₈ cycloalkyl as defined herein unsubstituted or substituted with one or more groups independently selected from hydroxy, carboxy, C₁₋₆ alkoxy, C₁₋₆ alkyl, halogen, carboxamide, trifluoromethyl, hydroxymethyl, and hydroxy(C₁-C₄)alkyl.

15 As used herein, the term "saturated heterocycle" is taken to be a 4-9 membered ring containing nitrogen and optionally one other atom selected from oxygen, nitrogen, and sulfur. The term "optionally substituted saturated heterocycle" is taken to be a saturated heterocycle as defined herein unsubstituted or substituted with one or more groups independently selected from hydroxy, carboxy, C₁₋₆ alkoxy, C₁₋₆ alkyl, halogen, carboxamide, trifluoromethyl, hydroxymethyl, and hydroxy(C₁-C₄)alkyl.

20 As used herein, the term "C₁-C₆ alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, pentyl, isopentyl, and hexyl. The term "C₁-C₆ alkyl" includes within its definition the terms "C₁-C₄ alkyl" and "C₁-C₃ alkyl."

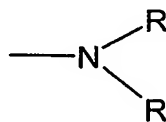
25 "C₁-C₆ alkenyl" refers to a straight or branched, divalent, unsaturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to, methylenyl, ethylenyl, propylenyl, isopropylenyl, butylenyl, isobutylenyl, *t*-butylenyl, pentylenyl, isopentylenyl, hexylenyl.

30 "C₁-C₆ alkoxy" represents a straight or branched C₁-C₆ alkoxy chain, as defined above, that is attached via the oxygen atom to a carbonyl moiety. Typical C₁-C₆

-13-

alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, *t*-butoxycarbonyl and the like.

The term "di(C₁-C₆ alkyl)amino" refers to a group of the formula:



5 wherein each R group independently represents a "C₁-C₆ alkyl" group, as defined above.

An "optionally substituted phenyl" is a phenyl ring that is unsubstituted or substituted with 1 to 5 substituents, more preferably 1 to 3 substituents, for example: halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylamino, trifluoromethyl, nitro, and cyano.

10 An "optionally substituted benzyl" is a benzyl ring that is unsubstituted or substituted with 1 to 5 substituents, more preferably 1 to 3 substituents, for example: halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, and cyano.

"Phenoxycarbonyl" refers to the group: phenyl-O-C(O)-. "Aryl" refers to an unsaturated aromatic carbocyclic group of 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthracenyl).

15 Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with 1 to 5 substituents, more preferably 1 to 3 substituents, selected from the group consisting of halo, hydroxy, acetyl, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, di(C₁-C₆ alkyl)amino, trifluoromethyl, trifluoromethoxy, -S(O)_m-(C₁-C₆ alkyl), and -S(O)_m-(phenyl), wherein m can be 0, 1, or 2.

"Arylalkyl" refers to aryl groups attached to alkyl groups, preferably having 1 to 6 carbon atoms in the alkyl moiety and 6 to 10 carbon atoms in the aryl moiety. Such arylalkyl groups are exemplified by benzyl, phenethyl, and the like.

25 Unless otherwise constrained by the definition for arylalkyl, such arylalkyl groups can be optionally substituted with 1 to 5 substituents, more preferably 1 to 3 substituents, selected from the group consisting of halo, hydroxy, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy, di(C₁-C₆ alkyl)amino, trifluoromethyl, trifluoromethoxy, carbamoyl, pyrrolidinyl, -S(O)_m-(C₁-C₆ alkyl), and -S(O)_m-(phenyl), wherein m can be 0, 1, or 2.

The arylalkyl groups may be optionally substituted on the aryl moiety, the alkyl moiety, or both the aryl moiety and the alkyl moiety.

The term "heterocycle" represents an unsubstituted or substituted 5- to 7-membered monocyclic, or 7- to 11-membered bicyclic heterocyclic ring that is saturated or unsaturated and that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and including a bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring to another heterocycle as defined above.

The term "heteroaryls" represents the above-defined heterocyclic rings that are fused to a benzene ring to another heterocycle as defined above.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocycles can be optionally substituted with 1 to 8 substituents selected from the group consisting of halo, nitro, cyano, hydroxy, acetyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₁₀ cycloalkyl, optionally substituted phenyl, phenethyl, phenoxy, phenoxycarbonyl, optionally substituted benzyl, 1,1-diphenylmethyl, oxo, C₁-C₆ alkoxycarbonyl, (C₁-C₆ alkoxy)C₁-C₆ alkyl-, trifluoromethyl, pyridyl, (pyrrolidinyl)C₁-C₆ alkyl-, and (pyridyl)C₁-C₆ alkyl-, di(C₁-C₆ alkyl)amino, trifluoromethyl, trifluoromethoxy, -S(O)_m-(C₁-C₆ alkyl), and -S(O)_m-(phenyl), wherein m can be 0, 1, or 2.

Examples of such heterocycles include azepinyl, azetidiny, benzazepinyl, benzimidazolyl, benzoazolyl, benzodioxolyl, benzodioxanyl, benzopyranyl, benzothiazolyl, benzothienyl, dihydropyrazolooxazinyl, dihydropyrazolooxazolyl, furyl, imidazolyl, imidazoliny, imidazolidinyl, indoliny, indolyl, isoindoliny, isoquinoliny, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholiny, naphthyridiny, oxadiazolyl, oxazolyl, oxazolidinyl, phthalimidyl, piperazinyl, piperidinyl, pyrazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazoliny, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolidinyl, pyrrolopyrazolyl, pyrrolyl, quinazoliny, quinoliny, quinuclidiny, tetrahydrofuryl, tetrahydropyranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, thiazolyl, thiazoliny, thiazolidinyl, thiadiazolyl, thienyl, thiomorpholiny, triazolyl, and the like.

Preferred heterocycles include: benzodioxolyl, dihydropyrrolopyrazolyl, pyridyl, quinolinyl.

The preceding paragraphs may be combined to define additional preferred classes
5 of compounds.

The compounds of Formula I are useful for the treatment of disorders of mammals, and the preferred mammal is a human.

The skilled artisan will appreciate that the introduction of certain substituents will create asymmetry in the compounds of Formula I. The present invention contemplates all
10 enantiomers and mixtures of enantiomers, including racemates. It is preferred that the compounds of the invention containing chiral centers are single enantiomers. The present invention further contemplates all diastereomers.

COMPOUNDS EXEMPLIFIED IN THE APPLICATION INCLUDE THE

15 FOLLOWING:

4-[2-(6-Ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid methyl ester,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-6-carboxylic
20 acid methyl ester,

4-(5-Benzyl-2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline-7-carboxylic
acid methyl ester,

3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-6-
carboxylic acid (2-dimethylamino-ethyl)-amide,

25 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-6-carboxylic
acid (2-dimethylamino-ethyl)-amide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (2-dimethylamino-ethyl)-amide,

5-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-benzofuran-2-
30 carboxylic acid (2-dimethyl amino-ethyl)-amide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide,

- 4-[2-(6-Methoxy-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
4-[2-(6-Ethoxy-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
3-(4-Fluoro-phenyl)-2-(6-methoxy-pyridin-2-yl)-pyrazolo[1,5-a]pyridine,
2-(6-Ethoxy-pyridin-2-yl)-3-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyridine,
5 7-Benzyl-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-
acrylic acid methyl ester,
3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-
acrylic acid,
10 4-[2-(6-Ethylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
4-[2-(6-Phenylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
4-[2-(6-Morpholin-4-yl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
3-(4-Fluoro-phenyl)-2-(6-methylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine,
3-(4-Methylsulfanyl-phenyl)-2-(6-methylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-
15 a]pyridine,
Dimethyl-(2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-
7-ylsulfanyl}-ethyl)-amine,
2-(Pyridin-2-yl)-3-(quinolin-4-yl)-pyrazolo[1,5-a]pyridine-5-carboxylic acid
dimethylamide,
20 2-(Pyridin-2-yl)-3-(quinolin-4-yl)-pyrazolo[1,5-a]pyridine-6-carboxylic acid
dimethylamide,
4-[2-(6-Vinyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
6-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-imidazo[1,2-a]pyridin-
2-yl-amine,
25 6-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-1H-benzoimidazol-2-
yl-amine,
[3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-6-yl]-
methanol,
6-Allyloxymethyl-3-(4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-
30 a]pyridine,
4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (3-pyrrolidin-1-yl-propyl)-amide,

3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-
propionamide,

3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-N-
(3-pyrrolidin-1-yl-propyl)-propionamide,

5 N-(2-Dimethylamino-ethyl)-3-{4-[2-(6-methyl- pyridin-2-yl)-pyrazolo[1,5-
a]pyridin-3-yl]-quinolin-7-yl}-propionamide,

2-Pyridin-2-yl-3-quinolin-4-yl-pyrazolo[1,5-a]pyridine-5-carboxylic acid (3-
dimethylamino-propyl)-amide,

10 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (2-hydroxy-ethyl)-amide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid hydrazide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (3-hydroxy-propyl)-amide,

15 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid methylamide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (3-ethoxy-propyl)-amide,

20 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (3-morpholin-4-yl-propyl)-amide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (3-imidazol-1-yl-propyl)-amide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (3-dimethylamino-propyl)-amide,

25 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid [2-(2-methoxy-phenyl)-ethyl]-amide,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid (2-morpholin-4-yl-ethyl)-amide,

30 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic
acid amide,

Dimethyl-(3-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-
7-yloxy}-propyl)-amine,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(2-morpholin-4-yl-ethoxy)-quinoline,

Diisopropyl-(2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}-ethyl)-amine,

5 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(2-pyrrol-1-yl-ethoxy)-quinoline,

Dimethyl-(1-methyl-2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}ethyl)-amine,

10 Methyl-(3-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl-oxy}-propyl)-amine,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(2-piperidin-1-yl-ethoxy)-quinoline,

Diethyl-(2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}-ethyl)-amine,

15 Dimethyl-{3-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-propyl}-amine,

7-(2-Morpholin-4-yl-ethoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline,

20 Diisopropyl-{2-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-ethyl}-amine,

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(3-morpholin-4-yl-propoxy)-quinoline,

1-(3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-yl]-quinolin-7-yloxy}-propyl)-1,3-dihydro-benzoimidazol-2-one

25 3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-propionic acid methyl ester,

Diethyl-{3-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-propyl}-amine,

30 Ethyl-methyl-{3-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-propyl}-amine,

4-(2-Pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-7-(3-pyrrolidin-1-yl-propoxy)-quinoline,

7-(3-Piperidin-1-yl-propoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline,

Diethyl-{2-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-ethyl}-amine,

5 Dimethyl-{2-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-ethyl}-amine,

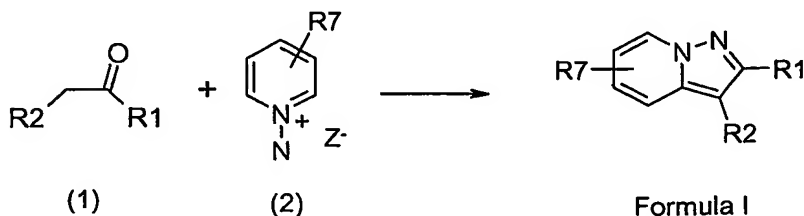
and the pharmaceutically acceptable salts, esters and prodrugs thereof.

10 The compounds exemplified above are merely representative of the invention and are not limiting in any fashion.

The compounds of the present invention can be prepared by a variety of procedures, some of which are illustrated in the Schemes below. It will be recognized by one of skill in the art that the individual steps in the following schemes may be varied to provide the compounds of Formula I. Some of these variations are discussed below.

The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties. Some substituents have been eliminated in the following schemes for the sake of clarity, and are not intended to limit the teaching of the schemes in any way.

SCHEME I

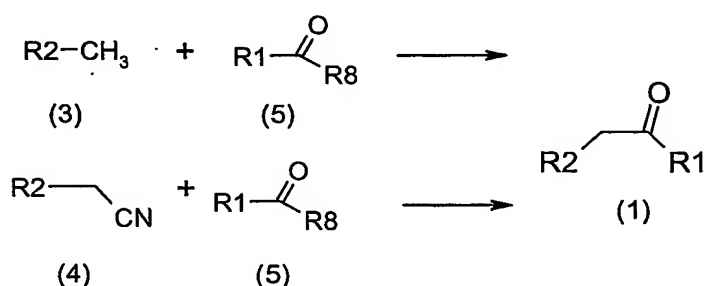


25

Scheme I, depicts a cyclization of optionally substituted 1-amino-pyridinium salts of formula (2), and optionally substituted ethanones of formula (1) in the formation of Formula I. Cyclization reaction of the optionally substituted ethanones of formula (1) with the 1-amino-pyridinium salt, in which the counter-anion, Z, can be a halogen or a

trialkyl-benzenesulfonate, are generally done with an organic base, such as triethylamine, DBU, or preferably diisopropylethylamine, in a suitable solvent such as ethanol under elevated temperatures. The product of Formula I can be isolated and purified by techniques well known in the art, such as precipitation, filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

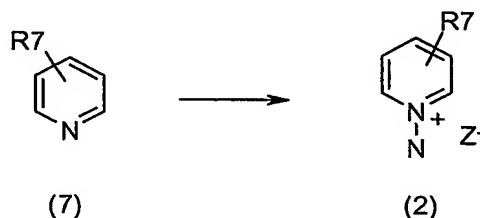
SCHEME II



Scheme II depicts an acylation of an appropriate aromatic and/or heteroaromatic compound of formula (3) and an appropriate carbonyl compound of formula (5) to give a compound of formula (1). The aromatic and/or heteroaromatic compounds of formula (3) are commercially available or can be produced by methods known in the art. The acylation of formula (3) requires that R⁸, of formula (5), be a suitable leaving group, such as C1-C6 alkoxy, disubstituted amino, halo, C1-C6 thioether, preferably disubstituted amino. The reaction is typically carried out in the presence of a suitable base that can create an anion of the compound of formula (3), such as lithium diisopropylamide, potassium bis(trimethylsilyl)amide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, sodium hydride, lithium hydride, potassium hydride, sodium alkoxides (sodium methoxide, or sodium ethoxide) or potassium alkoxides (potassium methoxide, or potassium ethoxide), with potassium bis(trimethylsilyl)amide being the preferred base. Generally, the reaction is carried out in suitable solvents, such as tetrahydrofuran and toluene or a combination of such, at temperatures of about -78 °C to ambient temperature. The product, formula (1), can be isolated and purified by techniques well known in the art, such as precipitation, filtration, extraction, evaporation, trituration, chromatography, and recrystallization. Another variation of the acylation is to use a nitrile compound of formula (4) in place of the aromatic- or heteroaromatic-methyl

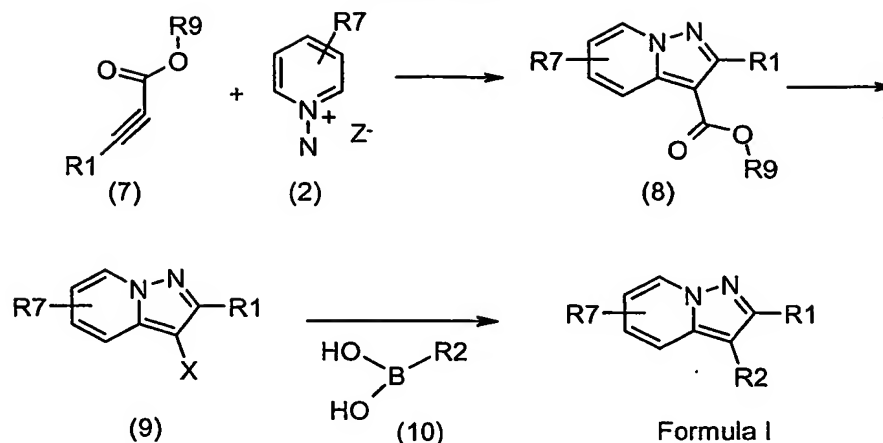
compounds of formula (3). The intermediate, cyanoketone, can be transformed to formula (1) by hydrolysis of the nitrile group and then subsequent decarboxylation. Generally, the cyanoketone is dissolved in a hydrogen halide acid solution, preferably hydrogen chloride. The reaction is carried out at temperatures of about ambient to refluxing for about 24 hours. This type of reaction is well known and appreciated in the art (Larock, R. C., *Comprehensive Organic Transformations*, copyright 1989, VCH, pp 993). Compounds of formula (4) can be acquired by treatment of an appropriate substituted aromatic- or heteroaromatic-methyl group with a halogenating reagent, such as N-halosuccinimides, preferably N-bromosuccinimide in carbon tetrachloride and subsequently reacting the aromatic-halomethylene intermediate with a nitrile source, such as lithium cyanide, potassium cyanide, or trimethylsilyl cyanide, preferably sodium cyanide. The reaction is carried out at ambient temperatures for about 24 hours to afford the acetonitrile compounds of formula (4), (Larock, R. C., *Comprehensive Organic Transformations*, copyright 1989, VCH, pp 313; Eur. J. Org. Chem. 1999, 2315-2321).

SCHEME III



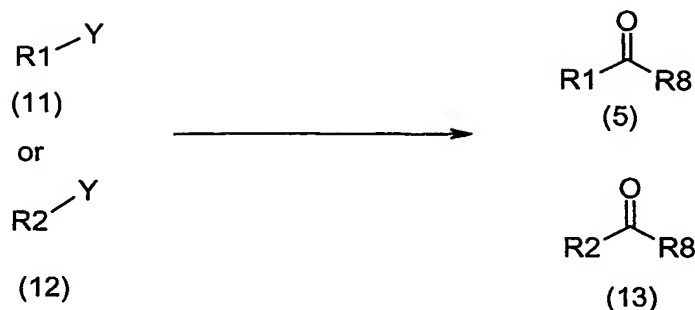
20 In Scheme 1, optionally substituted 1-amino-pyridinium salts of formula (2) are employed in the formation of Formula I. These salts are either commercially available or may be prepared by generally combining the appropriate substituted pyridine of formula (7) with a trialkyl-benzenesulfonylhydroxylamine preferably O-(2,4,6-trimethyl-benzenesulfonyl)-hydroxylamine in a suitable solvent such as dichloromethane. These
25 salts can be isolated and purified by precipitation with a nonpolar solvent such as hexanes.

SCHEME IV



To further elaborate substitution for compounds of Formula I at the R2 functionality, Scheme IV can be followed. Scheme IV depicts the formation of the pyrazolopyridine nucleus by cyclization of an appropriate substituted propynoic carboxyl-
 5 ester, followed by a typical hydrolysis of the ester (Larock, R. C., Comprehensive Organic Transformations, 2nd Ed., copyright 1999, John Wiley & Sons, pp 1959-1968) to the carboxylic acid, and a halodecarboxylation Reference to give formula (9), where X is a halogen. The cyclization procedure is similar to the one previously described in
 10 Scheme I, with the exception that the preferable base is DBU and the solvent should be acetonitrile. With a halogen at the C3 position of the pyrazolopyridine ring a coupling reaction with a boronic acid derivative of formula (10) can be conducted. This type of coupling reaction is well known in the art (Larock, R. C., Comprehensive Organic Transformations, 2nd Ed., copyright 1999, John Wiley & Sons, pp 104-107).

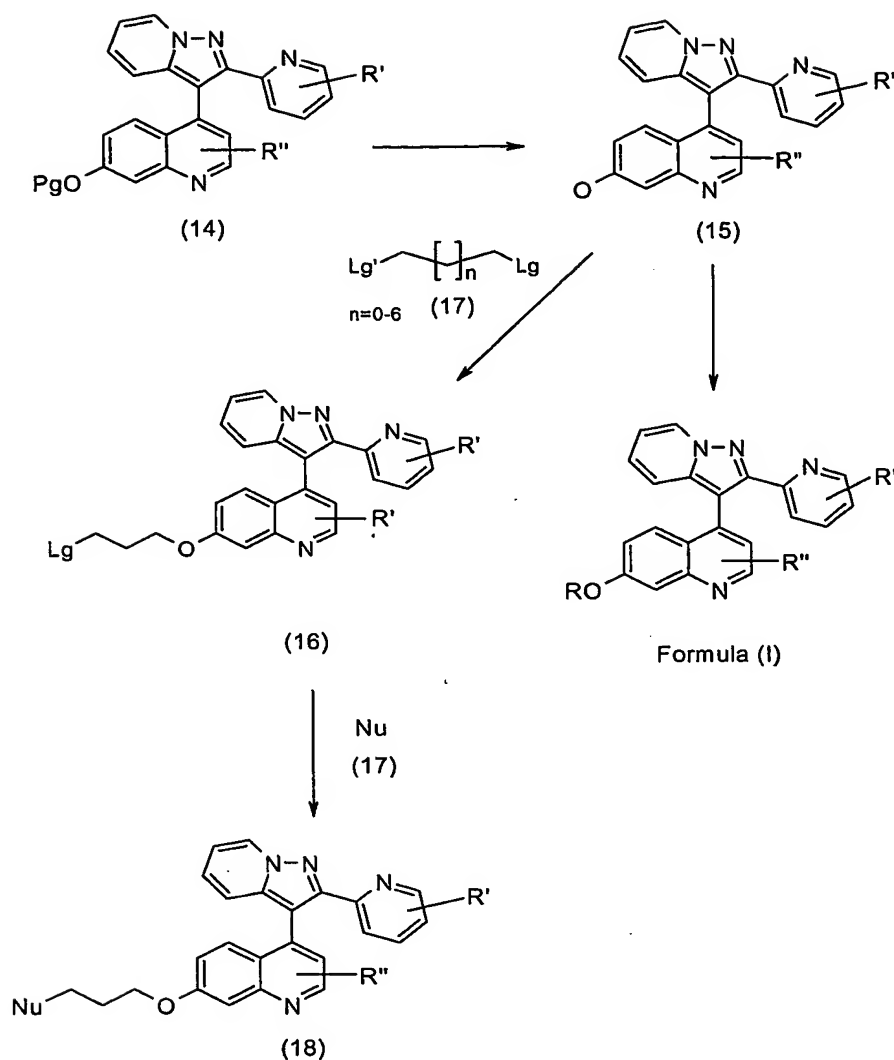
-23-

SCHEME V

Scheme V, depicts a carbonylation reaction for the formation of compounds of formula (5) and (13), where R8 is a suitable leaving group such as C1-C6 alkoxy, disubstituted amino, halo, C1-C6 thioether, preferably C1-C6 alkoxy. Compounds of formula (11) and (12) are used in the formation of formula (5) and (13), respectively. The carbonyl group of formula (5) and (13) can further undergo a synthetic transformation to interconvert between the leaving groups R8, where R8 is previously described. The Y group can be an aromatic or heteroaromatic halide and the reaction can be carried out in the presence of carbon monoxide, a suitable nucleophile, such as an amine or an alcohol, with a palladium (0) or palladium (II) catalyst, such as 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II): dichloromethane, tetrakis(triphenylphosphine)-palladium(0), bis(triphenylphosphine)palladium (II) chloride or palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), tris-(benzylideneacetone)dipalladium(0), palladium dichloride, palladium bis(trifluoroacetate), or preferably 1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II):dichloromethane. All reagents of the reagents are combined in a suitable solvent, typically tetrahydrofuran, toluene or ethylene glycol dimethyl ether, stirred at temperatures of about 0 to 80 °C. All products can be isolated and purified by techniques described above.

-24-

SCHEME VI



Scheme VI depicts the manipulation of hydroxy-aryl compounds of formula (15) for further alkylations and transformations to enable the scope of this invention, where the R group(s) are previously described. Representative conversions are shown in Scheme VI.

Scheme VI, depicts the deprotection of a protected aromatic-hydroxy group of formula (14) to give a compound of formula (15), where the "Pg" can be an alkoxide. The deprotection is well known and appreciated in the art (Greene T. W., Wuts, P. G. M. *Protective Groups in Organic Synthesis*, copyright 1991, John Wiley and Sons, Inc., pp146-149). The product of formula (15) can be isolated and purified by techniques previously described.

Scheme VI also depicts the transformation of an aryl ether compound of formula (15) to give the compounds of Formula (I). The formation of an aryl ether is well known and appreciated in the art (March, J., *Advanced Organic Chemistry*, copyright 1985, John Wiley and Sons, Inc., pp342-343, 589. and Mundy, B. P., Eller, M. G. *Name Reactions and Reagents in Organic Synthesis*, copyright 1988, John Wiley and Sons, Inc., pp 242, 530; Sawyer, J.S., Schmittling, E.A., Palkowitz, J.A., Smith, III, W.J., *J. Org. Chem.*, 1998, 63, 6338-6343). The products can be isolated and purified by techniques described above.

Scheme VI furthermore depicts an alkylation of a compound of formula (15) to give a variably substituted compound of formula (16), where the leaving group(s) "Lg" and "Lg'" can include such leaving groups, but are not limited to, halides, oxonium ions, alkyl perchlorates, ammonioalkanesulfonate esters, alkyl fluorosulfonates, nonaflates, tresylates, triflates, and sulfonic esters, preferably the mesylate or tosylate, given "Lg" and "Lg'" are not the same group. Typically, the appropriate compound of formula (15) is reacted with a suitable base that can form the anion of the phenol, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, lithium hydride, potassium hydride, with cesium carbonate being the preferred base, in the presence of a compound of formula (17). The reaction is carried out in a suitable solvent, such as tetrahydrofuran, dimethylsulfoxide, dimethyl acetamide or toluene, or preferably *N,N*-dimethylformamide at temperatures of about 0 to 100 °C. The products can be isolated and purified by techniques described above.

Finally, Scheme VI, depicts the nucleophilic substitution of leaving group "Lg", by a nucleophile to form a compound of the formula (16). Nucleophilic substitution is well known and appreciated in the art (March, J., *Advanced Organic Chemistry*, copyright 1985, John Wiley and Sons, Inc., pp 255-446). Typically, the compound of formula (16) is reacted with a nucleophile of formula (17), which is typically, but not limited to, primary amines, secondary amines, alcohols or thiols. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, dimethylsulfoxide, dimethyl acetamide or toluene, or preferably *N,N*-dimethylformamide at temperatures of about 0 to 100 °C. The products can be isolated and purified by techniques described above.

A skilled artisan can appreciate several transformations that can be applied to the synthetic process for production of useful and reactive intermediates. Further elaboration

can be completed by transformation of the appropriate functional groups, such as transformation of a carboxylester to an amide, halogen alkoxy exchange (Larock, R. C., Comprehensive Organic Transformations, 2nd Ed., copyright 1999, John Wiley & Sons, pp 893-894), hydrolysis of a carboxylester (Larock, R. C., Comprehensive Organic Transformations, 2nd Ed., copyright 1999, John Wiley & Sons, pp 1959-1968), palladium promoted additions (Larock, R. C., Comprehensive Organic Transformations, 2nd Ed., copyright 1999, John Wiley & Sons, pp 1685-1687), O-alkylations (Larock, R. C., Comprehensive Organic Transformations, 2nd Ed., copyright 1999, John Wiley & Sons, pp 890-893) and a nucleophilic exchange of aromatic-halogens (Larock, R. C., Comprehensive Organic Transformations, 2nd Ed., copyright 1999, John Wiley & Sons, pp 779-780). These types of transformations of functional groups are well known and appreciated in the art.

A skilled artisan would also appreciate that amine containing intermediates can be protected with various protecting groups such as a formyl group, acetyl, or preferably a tert-butoxycarbonyl moiety. Techniques for the introduction of these groups are well known to the skilled artisan. The skilled artisan will appreciate that the nitrogen-protecting groups may be removed at any convenient point in the synthesis of the compounds of the present invention. Methods of formation and removal of an amino-protecting group are well known in the art (for example, see: T.W. Greene, "Protective Groups in Organic Synthesis," John Wiley and Sons, New York, N.Y., 1991, Chapter 7).

The skilled artisan would appreciate that appropriate leaving groups for the hydroxy intermediates could include halides, oxonium ions, alkyl perchlorates, ammonio-alkanesulfonate esters, alkyl fluorosulfonates, nonaflates, tresylates, triflates, and sulfonic esters, preferably the mesylate or tosylate. Techniques for the introduction of these groups are well known to the skilled artisan. (See for example: March, "Advanced Organic Chemistry," John Wiley and Sons, New York, N.Y., 1992, pg. 352-362). The hydroxy compound is then dissolved in an appropriate solvent, such as tetrahydrofuran, diethyl ether or N,N-dimethylformamide and is reacted with a strong base, such as potassium hydride or sodium hydride. The reaction is conducted under nitrogen at about 0°C and stirred for 30-120 minutes. These compounds can be isolated and purified by standard techniques.

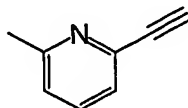
Many of the compounds of the present invention are not only inhibitors of TGF-beta, but are also useful intermediates for the preparation of additional compounds of the present invention. For example, secondary amines may be acylated, alkylated or coupled with simple carboxylic acids or amino acids under standard conditions. Furthermore, ester moieties may be reduced to the corresponding alcohols. These alcohols may then be activated and displaced by a number of nucleophiles to provide other compounds of the invention. The skilled artisan will also appreciate that not all of the substituents in the compounds of Formula I will tolerate certain reaction conditions employed to synthesize the compounds. These moieties may be introduced at a convenient point in the synthesis, or may be protected and then deprotected as necessary or desired. Furthermore, the skilled artisan will appreciate that in many circumstances, the order in which moieties are introduced is not critical.

The following preparations and examples further illustrate the preparation of compounds of the present invention and should not be interpreted in any way as to limit the scope. Those skilled in the art will recognize that various modifications may be made while not departing from the spirit and scope of the invention. All publications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains.

The terms and abbreviations used in the instant Preparations and Examples have their normal meanings unless otherwise designated. For example "°C", "N", "mmol", "g", "mL", "M", "HPLC", "IR", "MS(FD)", "MS(IS)", "MS(FIA)", "MS(FAB)", "MS(EI)", "MS(ES)", "UV", and "¹H NMR", refer to degrees Celsius, normal or normality, millimole or millimoles, gram or grams, milliliter or milliliters, molar or molarity, high performance liquid chromatography, infrared spectrometry, field desorption mass spectrometry, ion spray mass spectrometry, flow injection analysis mass spectrometry, fast atom bombardment mass spectrometry, electron impact mass spectrometry, electron spray mass spectrometry, ultraviolet spectrometry, and proton nuclear magnetic resonance spectrometry, respectively. In addition, the absorption maxima listed for the IR spectra are only those of interest and not all of the maxima observed.

PREPARATION 1

2-Ethynyl-6-methyl-pyridine



2-Bromo-6-methylpyridine (0.5 g, 2.9 mmol) and trimethylsilylacetylene (0.29 g, 2.9 mmol) in Et₃N (15 mL) is purged with argon. Then CuI (11 mg, 0.06 mmol) and (PPh₃)₂PdCl₂ (42 mg, 0.06 mmol) are added and the reaction stirred under argon at room temp for 2 hours. The solvent is removed in vacuo and the residue diluted in EtOAc (50 mL) and water (50 mL). The organic is separated and washed with brine. The solvent is removed to afford a dark oil. This oil is diluted in MeOH (50 mL) and treated with a 1 N NaOH solution (10 mL) and stirred for 3 hours at room temp. The aqueous is then acidified to pH=4 with 1 N HCl and extracted with dichloromethane. The solvent is removed in vacuo to afford 1.16 g (24%) as a light yellow oil used as is in following reactions. ¹H NMR (CDCl₃) δ: 7.54 (t, 1H), 7.29 (d, 1H), 7.12 (d, 1H), 3.12 (s, 1H), 2.55 (s, 1H). MS ES⁺ m/e 118.1 (M+1).

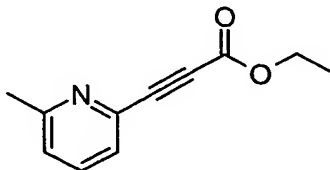
By method in PREPARATION 1 the following compounds were synthesized:

PREP #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
2	2-Ethynylpyridine	2-Bromopyridine		MS ES ⁺ m/e 103.9 (M+1).	
3	2-Ethyl-6-ethynyl-pyridine	2-Bromo-6-ethylpyridine		MS ES ⁺ m/e 133.0 (M+1).	

-29-

PREPARATION 4

(6-Methyl-pyridin-2-yl)-propynoic acid ethyl ester



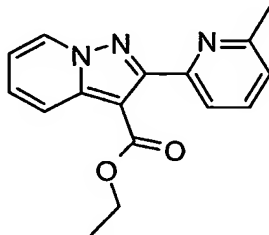
A solution of 2-Ethynyl-6-methyl-pyridine (0.5 g, 4.3 mmol) in THF (20 mL) is
 5 cooled to -78 °C and treated with 1.6 M n-butyllithium in hexanes (2.9 mL, 4.7 mmol)
 and stirred for 0.5 hours. This solution is then treated with ethyl chloroformate (2.85 mL,
 30 mmol) and stirred for 3 hours while the solution warms to room temperature. The
 reaction is diluted with saturated aqueous ammonium chloride and extracted with EtOAc.
 The solvent is concentrated to afford 0.67 g (83%) of desired product as a light yellow oil.
 10 UV (95% EtOH) λ_{max} 286 nm (ϵ 10977), 238 nm (ϵ 9757). TOF MS ES⁺ exact mass
 calculated for C₁₁H₁₁NO₂ (p+1): m/z = 190.0868. Found: 190.0864.

By method in PREPARATION 4 the following compounds were synthesized:

PREP #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
5	Pyridin-2-yl-propynoic acid ethyl ester	2-Ethynylpyridine (Prep. 2)		MS ES ⁺ m/e 176.2 (M+1).	
6	(6-Ethyl-pyridin-2-yl)-propynoic acid ethyl ester	2-Ethyl-6-ethynyl-pyridine (Prep. 3)		MS ES ⁺ m/e 204.1 (M+1).	

PREPARATION 7

2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester



- A solution of (6-methyl-pyridin-2-yl)-propynoic acid ethyl ester (0.62 g, 3.3 mmol) and 1-aminopyridinium iodide (0.8 g, 3.6 mmol) in acetonitrile (15 mL) is treated with DBU (0.5 mL, 3.3 mmol) and heated to reflux for 0.5 hours. The reaction is concentrated to a dark solid and purified by silica gel column chromatography (1:1 hexane/ethyl acetate) to afford 0.224 g (24%) of desired product as a yellow solid. MS ES⁺ m/e 282.2 (M+1). UV (95% EtOH) λ_{\max} 275 nm (ϵ 13005), 234 nm (ϵ 26550), 225 nm (ϵ 26057). TOF MS ES⁺ exact mass calculated for C₁₁H₁₁NO₂ (p+1): m/z = 282.1243. Found: 282.1244. Anal. Calcd for C₁₆H₁₅N₃O₂: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.04; H, 5.28; N, 14.65.

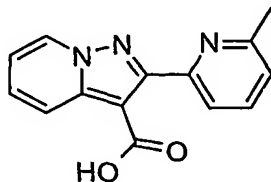
PREP #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
8	2-(6-Methyl-pyridin-2-yl)-6-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester (Isomer 1) and 2-(6-Methyl-pyridin-2-yl)-4-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester (Isomer 2)	(6-Methyl-pyridin-2-yl)-propynoic acid ethyl ester (Prep. 4)	1-Amino-3-phenyl pyridinium	¹ H NMR of Isomer 1 (CDCl ₃) δ 8.79 (s, 1H), 8.27 (d, 1H), 7.73-7.59 (m, 5H), 7.53-7.42 (m, 3H), 7.23 (d, 1H), 4.31 (q, 2H), 2.68 (s, 3H), 1.30 (t, 3H) and ¹ H NMR of Isomer 2 δ 8.54 (d, 1H), 7.74 (d, 1H), 7.65 (t, 1H),	When treated with 3-substituted aminated pyridine, reaction gave mixture of products with 4 or 6 substitution

PREP #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
				7.44 (m, 5H), 7.16 (m, 2H), 6.96 (t, 1H), 3.69 (q, 2H), 2.57 (s, 3H), 0.92 (t, 3H)	
9	6-Methanesulfonyl-2-(6-methylpyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester and 4-Methanesulfonyl-2-(6-methylpyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester	(6-Methylpyridin-2-yl)-propynoic acid ethyl ester (Prep. 4)	1-Amino-3-methanesulfonyl pyridinium iodide	MS ES ⁺ m/e 360.1(M+1).	When treated with 3-substituted aminated pyridine, reaction gave mixture of products with 4 or 6 substitution. Mixture could be separated by chromatography
10	2-Pyridin-2-yl-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester	Pyridin-2-yl-propynoic acid ethyl ester (Prep. 5)	1-Aminopyridinium iodide	MS ES ⁺ m/e 268.1 (M+1).	
11	2-(6-Ethylpyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester	(6-Ethylpyridin-2-yl)-propynoic acid ethyl ester (Prep. 6)	1-Aminopyridinium iodide	MS ES ⁺ m/e 296.1 (M+1).	

-32-

PREPARATION 12

2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid

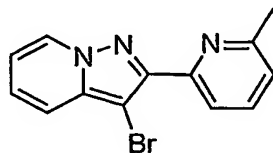


A solution of 2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester (0.18 g, 0.6 mmol) in EtOH (10 mL) is treated with a 2N NaOH solution (3 mL) and refluxed for 3 hours. The reaction is concentrated to a yellow solid and diluted with 1N HCl (30 mL). The aqueous is extracted with CH₂Cl₂ (3 x 10 mL) and the organic solution dried over Na₂SO₄. The solution is filtered and the solvent removed in vacuo to afford 0.152 g (94%) of desired product as a white solid. MS ES⁺ m/e 254.1 (M+1). UV (95% EtOH) λ_{\max} 284 nm (ϵ 23625), 244 nm (ϵ 24036). TOF MS ES⁺ exact mass calculated for C₁₄H₁₁N₃O₂ (p+1): m/z = 254.0930. Found: 254.0919. Anal. Calcd for C₁₄H₁₁N₃O₂: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.22; H, 4.42; N, 16.25.

PREP #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
13	2-(6-Methyl-pyridin-2-yl)-6-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid and 2-(6-Methyl-pyridin-2-yl)-4-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid	2-(6-Methyl-pyridin-2-yl)-6-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester (Isomer 1) and 2-(6-Methyl-pyridin-2-yl)-4-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid ethyl ester (Isomer 2) (Prep. 8)		MS ES ⁻ m/e 328.1 (M-1).	Product was isolated as a mixture
14	6-Methanesulfonyl-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid	PREP. 9		MS ES ⁺ m/e 332.1 (M+1), MS ES ⁻ m/e 330.2 (M-1).	
15	2-Pyridin-2-yl-pyrazolo[1,5-a]pyridine-3-carboxylic acid	PREP. 10		MS ES ⁻ m/e 238 (M-1).	
16	2-(6-Ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid	PREP. 11		MS ES ⁻ m/e 266.1 (M-1).	

PREPARATION 17

3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine



- A solution of 2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid (0.92 g, 3.6 mmol), sodium bicarbonate (1.04 g, 12.4 mmol), and N-bromosuccinimide (0.71 g, 4.0 mmol) in DMF (25 mL) is stirred for 2 hours at room temperature. The reaction is then diluted with water (50 mL) and extracted with EtOAc (3 x 15 mL). The organic layer is washed with brine and dried over sodium sulfate. The solvent is removed in vacuo to afford 0.91 g (87%) of desired product as a dark green solid. UV (95% EtOH) λ_{\max} 282 nm (ϵ 12089), 233 nm (ϵ 21813). TOF MS ES⁺ exact mass calculated for C₁₃H₁₀BrN₃ (p+1): m/z = 288.0136. Found: 287.0058. Anal. Calcd for C₁₃H₁₀BrN₃: C, 54.19; H, 3.50; N, 14.58. Found: C, 54.10; H, 3.60; N, 14.48.

PREP #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
18	3-Bromo-2-(6-methyl-pyridin-2-yl)-6-phenyl-pyrazolo[1,5-a]pyridine	2-(6-Methyl-pyridin-2-yl)-6-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid and 2-(6-Methyl-pyridin-2-yl)-4-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid (Prep. 13)		MS ES ⁺ m/e 364.1, 366.1 (M+1).	Mixture was separated by Silica Gel chromatography: (hexanes, EtOAc)
19	3-Bromo-2-(6-methyl-pyridin-2-yl)-4-phenyl-pyrazolo[1,5-a]pyridine	2-(6-Methyl-pyridin-2-yl)-6-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid and		MS ES ⁺ m/e 364.1, 366.1 (M+1).	Mixture was separated by chromatography, as above

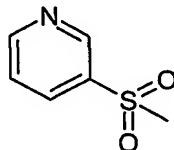
-35-

PREP #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
		2-(6-Methyl-pyridin-2-yl)-4-phenyl-pyrazolo[1,5-a]pyridine-3-carboxylic acid (Prep. 13)			
20	3-Bromo-6-methanesulfonyl-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	6-Methanesulfonyl-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid (Prep. 14)		Exact Mass calculated 365.9912, found 365.9923	
21	3-Bromo-2-pyridin-2-yl-pyrazolo[1,5-a]pyridine	2-Pyridin-2-yl-pyrazolo[1,5-a]pyridine-3-carboxylic acid (Prep. 15)		MS ES ⁺ m/e 273.9, 275.9 (M+1).	
22	3-Bromo-2-(6-ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	2-(6-Ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-carboxylic acid (Prep. 16)		MS ES ⁺ m/e 302.0, 304.0 (M+1).	

-36-

PREPARATION 23

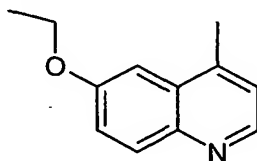
3-Methanesulfonyl-pyridine



To a solution of 3-bromopyridine (20 g, 127 mmol) in THF (200 ml) at room temperature. is added a solution of 2M isopropylmagnesium chloride in THF (64 ml, 127 mmol). The resulting mixture is stirred for 2 hours, treated with triethylamine (20 ml), immediately followed by methanesulfonylchloride (10 ml, 127 mmol) and the resulting mixture stirred for 18 hours at room temperature. The mixture is diluted with water (200 ml) and extracted with EtOAc (3 x 100 ml). The mixture is concentrated in vacuo and purified on Silica gel (eluting with 50/50 Hexane/ EtOAc). ¹H-NMR (CDCl₃) δ : 9.17 (s, 1H), 8.90 (d, 1H), 8.25 (dd, 1H), 7.55 (m, 1H), 3.12 (s, 3H).

PREPARATION 24

6-Ethoxy-4-methyl-quinoline



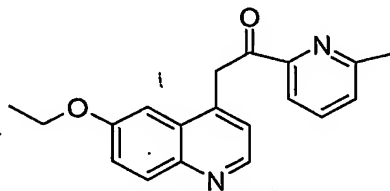
4-Ethoxyaniline (15 g, 109 mmol) in dissolved in dioxane (1L) and cooled to 0 °C in an ice bath. To this mixture is added H₂SO₄ (12 mL, 219 mmol) dropwise with stirring and heating at 100° C. Water (2 mL) is added followed by methyl vinyl ketone (13 mL, 163 mmol, in 125 mL of dioxane) dropwise over 2 hours. The mixture is heated for 1 hour after addition and then cooled. To the residue is added 1.5 eq of 1M aqueous Na₂CO₃ until the pH is 8. The organic layer is separated, condensed to an oil, and purified on silica gel (eluting with 50/50 hexane/EtOAc).

The desired product is isolated as a solid 6 g (30 %). TOF MS ES⁺ (M+1) 188.1079.

-37-

PREPARATION 25

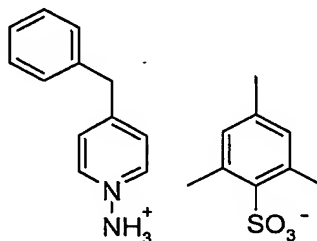
2-(6-Ethoxy-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone



To a solution of 6-ethoxy-4-methyl-quinoline (360 mg, 2.0 mmol) in THF at -78 °C add 1.5M lithium diisopropylamide (4.6 ml, 7.0 mmol) dropwise and stir for 1 hour. 6-Methyl-pyridine-2-carboxylic acid methoxy-methyl-amide (430 mg, 2.4 mmol) is then added, and the mixture stirred for 30 minutes at -78 °C before quenching with 1N HCl (5 ml). Neutralize with saturated aqueous NaHCO_3 and extract with EtOAc (3 x 50 ml). The organic phase is then dried with MgSO_4 and concentrated in vacuo. The crude product was chromatographed on silica gel (elute with 50/50 Hexane/EtOAc) to give 120 mg (20 %) of the title compound. MS ES^+ m/e 307.1 (M+1).

PREPARATION 26

4-Benzyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate



A solution of 4-benzyl pyridine (0.6 g, 3.5 mmol) in methylene chloride (5 ml) is cooled with ice bath. Freshly prepared O-(2,4,6-trimethyl-benzenesulfonyl)hydroxylamine (0.92 g, 4.2 mmol) in methylene chloride (5 ml) is added dropwise with stirring. The ice bath is removed and the mixture stirred for 1 hour, then concentrated in vacuo. The residue is dissolved in methylene chloride and precipitated with hexanes. The hexane layer is decanted. Concentration provides 1.0 g (62%) of the title compound as a viscous oil.

^1H NMR (CD_3OD) δ 8.63-8.53 (m, 2H), 7.84-7.71 (m, 2H), 7.41-7.22 (m, 5H), 6.85 (s, 2H), 4.21 (s, 2H), 2.60 (s, 6H), 2.22 (s, 3H).

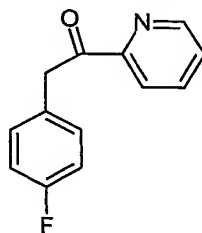
By the method of PREPARATION 26 the following compounds were prepared:

Prep. #	Product Name	Physical Data
27	1-Amino-3-phenyl-pyridinium-2,4,6-trimethyl-benzenesulfonic acid anion	¹ H-NMR (CDCl ₃): δ 9.24 (s, 1H), 9.01 (d, 1H, J=4Hz), 7.97 (d, 1H, J=2Hz), 7.68 (t, 1H, J=2Hz), 7.56 (d, 2H, J=4Hz), 7.38 (m, 2H), 6.79 (s, 2H), 2.63 (s, 6H), 2.19 (s, 3H).
28	1-Amino-4-phenyl-pyridinium-2,4,6-trimethyl-benzenesulfonic acid anion	¹ H-NMR (CDCl ₃): δ 8.97 (d, 2H, J=4Hz), 8.04 (d, 2H, J=4Hz), 7.72 (d, 2H, J=6Hz), 7.26 (m, 3H), 2.81 (s, 2H), 2.64 (s, 6H), 2.20 (s, 3H).
29	1-Amino-3-methanesulfonyl-pyridinium-2,4,6-trimethyl-benzenesulfonic acid anion	¹ H-NMR (CDCl ₃): δ 9.30 (s, 1H), 8.97 (d, 1H), 8.72 (d, 1H), 8.16 (t, 1H), 6.88 (s, 2H), 2.61 (s, 6H), 2.37 (s, 3H).
30	1-Amino-3-methoxycarbonyl-pyridinium-2,4,6-trimethyl-benzenesulfonic acid anion	¹ H-NMR (CDCl ₃): δ 9.43 (s, 2H), 8.40 (d, 1H), 7.78 (t, 1H), 6.82 (s, 2H), 3.93 (s, 3H), 2.63 (s, 6H), 2.24 (s, 3H).
31	4-Methoxycarbonyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate	¹ H NMR (CD ₃ OD): δ 8.84-8.79 (m, 2H), 8.39-8.31 (m, 2H), 6.84 (s, 2H), 4.01 (s, 3H), 2.59 (s, 6H), 2.22 (s, 3H).
32	3-Ethoxycarbonyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate	¹ H NMR (CD ₃ OD): δ 9.24 (s, 1H), 8.09-8.85 (m, 1H), 8.75-8.66 (m, 1H), 8.10-8.01 (m, 1H), 6.85 (s, 2H), 4.53-4.43 (m, 2H), 2.61 (s, 6H), 2.22 (s, 3H), 1.48-1.36 (m, 3H).
33	1-Amino-3-iodo-pyridinium-2,4,6-trimethyl-benzenesulfonic acid anion	¹ H-NMR (CDCl ₃): δ 9.06 (s, 1H), 8.71 (d, 1H), 8.57 (d, 1H), 7.67 (t, 1H), 6.86 (s, 2H), 2.61 (s, 6H), 2.23 (s, 3H).

PREPARATION 34

5

2-(4-Fluorophenyl)-1-pyridin-2-yl-ethanone



Combine a solution of 4-fluorophenylacetonitrile (1.00 g, 7.4 mmol) and ethyl picolinate (1.12 g, 7.4 mmol) in absolute ethyl alcohol (15 mL) under N₂ with 21 wt% sodium ethoxide solution in denatured ethyl alcohol (4.2 mL, 11.1 mmol) and heat to reflux for 2 hours, then pour onto ice. Adjust the pH to 4 with concentrated hydrochloric

10

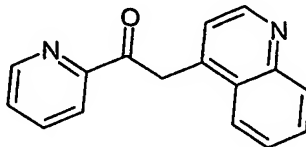
- acid and collect the precipitate by vacuum filtration. Dissolve the residue in 48 % aqueous hydrobromic acid (25 mL) and heat to reflux for 2 hours. Pour the solution onto ice and adjust the pH to 7 with 5N aqueous sodium hydroxide solution. Extract the aqueous solution three times with CH₂Cl₂. Combine the organic extracts, dry (Na₂SO₄),
- 5 filter, and concentrate in vacuo to afford the title compound 668 mg (42%) as a brown amorphous solid. MS FAB⁺ m/z = 216.1

By the method of PREPARATION 34 the following compounds were prepared:

Prep. #	Product Name	Physical
35	1-(6-Ethyl-pyridin-2-yl)-2-(4-fluoro-phenyl)-ethanone	¹ H-NMR (CDCl ₃) δ : 7.84 (d, 1H), 7.72 (t, 1H), 7.34-7.31 (m, 3H), 7.09-6.96 (m, 2H), 4.50 (s, 2H), 2.90 (q, 2H), 1.37 (t, 3H)
36	2-(4-Fluoro-phenyl)-1-(6-propyl-pyridin-2-yl)-ethanone	¹ H-NMR (CDCl ₃) δ : 7.85 (d, 1H), 7.72 (t, 1H), 7.31 (m, 3H), 7.00 (m, 2H), 4.51 (s, 2H), 2.85 (t, 2H), 1.83 (m, 2H), 1.00 (t, 3H)
37	1-(6-Ethyl-pyridin-2-yl)-2-(4-fluoro-naphthalen-1-yl)-ethanone	MS ES ⁺ m/e 294.1 (M+1).
38	2-(4-Fluoro-phenyl)-1-(6-methyl-pyridin-2-yl)-ethanone	MS ES ⁺ m/e 230.09 (M+1).
39	2-(4-Methoxy-phenyl)-1-pyridin-2-yl-ethanone	MS ES ⁺ m/e 228.09 (M+1).
40	1-Pyridin-2-yl-2-(4-trifluoromethyl-phenyl)-ethanone	MS ES ⁺ m/e 266.07 (M+1).
41	2-(3-Chloro-4-fluoro-phenyl)-1-(6-methyl-pyridin-2-yl)-ethanone	¹ H NMR (CDCl ₃) δ 7.86-7.83 (m, 1H), 7.73-7.71 (m, 1H), 7.42-7.33 (m, 2H), 7.26-7.04 (m, 2H), 4.49 (s, 2H), 2.65 (s, 3H).
42	1-(6-Methyl-pyridin-2-yl)-2-(2,4,5-trifluoro-phenyl)-ethanone	¹ H NMR (CDCl ₃) δ 7.87-7.85 (m, 1H), 7.75-7.70 (m, 1H), 7.37-7.34 (m, 1H), 7.15-7.07 (m, 1H), 6.98-6.89 (m, 1H), 4.55 (s, 2H), 2.64 (s, 3H)
43	2-(4-Fluoro-3-trifluoromethyl-phenyl)-1-(6-methyl-pyridin-2-yl)-ethanone	¹ H NMR (CDCl ₃) δ 7.86-7.84 (m, 1H), 7.74-7.62 (m, 2H), 7.53-7.49 (m, 1H), 7.36-7.33 (m, 1H), 7.16-7.10 (m, 1H), 4.55 (s, 2H), 2.65 (s, 3H)
44	1-(6-Chloro-pyridin-2-yl)-2-(4-fluoro-phenyl)-ethanone	¹ H NMR (CDCl ₃) δ 8.01-7.92 (m, 1H), 7.86-7.75 (m, 1H), 7.57-7.50 (m, 1H), 7.35-7.22 (m, 2H), 7.08-6.93 (m, 2H), 4.47 (s, 2H). TLC (SiO ₂): R _f 0.57 (30% ethyl acetate/hexanes)

PREPARATION 45

1-Pyridin-2-yl-2-quinolin-4-yl-ethanone



- To a solution of diisopropylamine (44.9 mL, 320 mmol) in THF (500 mL) at -78°
- 5 C add 1.6 M n-butyl lithium in hexane (200 mL, 320 mmol). Stir for 10 minutes and add dropwise a solution of lepidine (42.9 g, 300 mmol) in THF (200 mL) over 20 minutes at -78° C and quickly add a solution of ethyl picolinate (48.3 g, 320 mmol). Allow the reaction to warm slowly to 0° C and quench by pouring into water (1L). Add ethyl acetate (1L). Dissolve residual solids by adding Acetic acid (20 mL). Separate the layers
- 10 and extract the aqueous layer with one portion of ethyl acetate (100 mL). Combine the organic extracts, dry over sodium sulfate, and concentrate in vacuo. Triturate the crude oil with hexane/ether to give 36 g of the title compound. Concentrate the filtrate. Chromatograph the residue on silica gel (elute with 10:9:1 CH_2Cl_2 , ether, MeOH). Precipitate the purified product from ether/hexane to give 21 g of the title compound.
- 15 Combined yield: 57 g (76 %) of title compound as a yellow crystalline solid. MS ES^+ m/e 249.0 (M+1).

By the method of PREPARATION 45 the following compounds were prepared:

Prep. #	Product Name	Physical data	Comments
46	2-(6,7-Dimethoxy-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	MS ES^+ m/e 323.1 (M+1).	
47	2-(6-Ethoxy-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	MS ES^+ m/e 307.1 (M+1).	
48	1-Pyridin-2-yl-2-quinolin-4-yl-ethanone	MS ES^+ m/e 251 (M+1).	
49	2-(7-Ethoxy-quinolin-4-yl)-1-pyridin-2-yl-ethanone	$^1\text{H-NMR}$ (CDCl_3): δ 8.74 (d, 1H, J=4Hz), 7.97 (d, 1H, J=8Hz), 7.84 (d, 1H, J=8Hz), 7.71 (t, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz), 7.36 (s, 1H, J=4Hz), 7.26 (m, 1H, J=4Hz), 7.18 (d, 1H, J=4Hz), 4.97 (s, 2H, J=4Hz),	

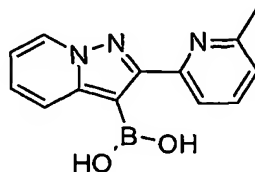
Prep. #	Product Name	Physical data	Comments
		4.18 (q, 2H, J=5Hz), 2.60 (s, 3H, J=4Hz), 1.48 (t, 3H, J=7Hz)	
50	2-(7-Ethoxy-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	MS ES ⁺ m/e 307.1 (M+1).	
51	1-(6-Methyl-pyridin-2-yl)-2-quinolin-4-yl-ethanone	MS ES ⁺ m/e 263.1 (M+1).	
52	1-(6-Ethyl-pyridin-2-yl)-2-quinolin-4-yl-ethanone	MS ES ⁺ m/e 277.33 (M+1).	
53	1-Furan-2-yl-2-quinolin-4-yl-ethanone	TOF MS exact mass m/z = 238.0868. Found: 238.0888.	
54	2-Quinolin-4-yl-1-thiophen-2-yl-ethanone	TOF MS exact mass m/z = 254.0640. Found: 254.0657.	
55	1-Pyridin-2-yl-2-pyridin-4-yl-ethanone	MS ES ⁺ m/e 199.2 (M+1).	KHMDS
56	2-(6-Ethoxy-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	MS ES ⁺ m/e 307.1 (M+1).	
57	1-(6-Chloro-pyridin-2-yl)-2-quinolin-4-yl-ethanone	¹ H NMR (CDCl ₃): δ 8.81 (m, 1H), 8.08 (m, 1H), 7.96 (m, 2H), 7.76 (m, 1H), 7.63 (m, 1H), 7.41 (m, 2H), 7.34 (m, 1H), 4.94 (s, 2H).	
58	1-(6-Fluoro-pyridin-2-yl)-2-quinolin-4-yl-ethanone	MS APCI ⁺ m/e 267 (M+1). TLC (SiO ₂): R _f 0.30 (1:2 acetone/hexanes)	
59	1-(5-Butyl-pyridin-2-yl)-2-quinolin-4-yl-ethanone	TLC (SiO ₂): R _f 0.40 (1:1 acetone/hexanes)	
60	2-(8-Fluoro-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	¹ H NMR (CDCl ₃) δ 8.90-8.85 (m, 1H), 7.90-7.70 (m, 2H), 7.50-7.30 (m, 3H), 5.05 (s, 2H), 2.70 (s, 3H).	KHMDS
61	1-(6-Methyl-pyridin-2-yl)-2-(6-trifluoromethyl-quinolin-4-yl)-ethanone	¹ H NMR (CDCl ₃) δ 8.97-8.94 (m, 1H), 8.55-8.51 (m, 1H), 8.25-8.20 (m, 1H), 7.98-7.93 (m, 1H), 7.89-7.83 (m, 1H), 7.77-7.69 (m, 1H), 7.54-7.50 (m, 1H), 7.41-7.32 (m, 1H), 5.00 (s, 2H), 2.69 (s, 3H).	
62	2-(7-Bromo-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	¹ H NMR (CDCl ₃) δ 8.85 (m, 1H), 8.30 (s, 1H), 8.00-7.60 (m, 4H), 7.45-7.35 (m, 2H), 5.05 (s, 2H), 2.65 (s, 3H).	
63	2-(7-Trifluoromethyl-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	¹ H NMR (CDCl ₃) δ 8.88 (m, 1H), 8.15-8.10 (m, 1H), 8.00 (s,	

Prep. #	Product Name	Physical data	Comments
	yl)-ethanone	¹ H), 7.98-7.80 (m, 2H), 7.75-7.65 (m, 1H), 7.50 (m, 1H), 7.35-7.33 (m, 1H), 5.00 (s, 2H), 2.70 (s, 3H)	
64	2-(6-Bromo-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	¹ H NMR (CDCl ₃) δ 8.89-8.81 (m, 1H), 8.40 (s, 1H), 8.03-7.99 (m, 1H), 7.90-7.85 (m, 1H), 7.79-7.67 (m, 2H), 7.49-7.38 (m, 2H), 4.97 (s, 2H), 2.71 (s, 3H)	
65	1-Pyridin-2-yl-2-quinolin-4-yl-ethanone	¹ H NMR (CDCl ₃) δ 8.85-8.80 (m, 1H), 8.10-8.00 (m, 2H), 7.85-7.87 (m, 1H), 7.73-7.60 (m, 2H), 7.50-7.43 (m, 1H), 7.40-7.30 (m, 2H), 5.00 (s, 2H)	KHMDS
66	2-(7-Bromo-quinolin-4-yl)-1-pyridin-2-yl-ethanone	¹ H NMR (CDCl ₃) δ 8.85 (m, 1H), 8.30 (s, 1H), 8.00-7.60 (m, 4H), 7.45-7.35 (m, 3H), 5.05 (s, 2H)	KHMDS
67	2-(7-Methoxy-quinolin-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	¹ H NMR (CDCl ₃) δ 8.79-8.72 (m, 1H), 8.01-7.96 (m, 1H), 7.90-7.83 (m, 1H), 7.79-7.70 (m, 1H), 7.49-7.42 (m, 1H), 7.40-7.37 (m, 1H), 7.30-7.24 (m, 1H), 7.23-7.20 (m, 1H), 5.05 (s, 2H), 3.94 (s, 3H), 2.70 (s, 3H).	KHMDS
68	2-(7-Methoxy-quinolin-4-yl)-1-pyridin-2-yl-ethanone	MS APCI ⁺ m/e 279 (M+1).	KHMDS
69	2-(7-Chloro-quinoline-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	mp 88-90 °C EA Calcd. for C ₁₇ H ₁₃ ClN ₂ O: C, 68.81; H, 4.41; O, 9.44; Found: C, 48.48; H, 4.38; N, 9.63	
70	2-(6,7-di-Fluoro-quinoline-4-yl)-1-(6-methyl-pyridin-2-yl)-ethanone	MS ES ⁺ m/e 299 (M+1).	
71	2-(6,7-di-Chloro-quinolin-4-yl)-1-6-ethyl-pyridin-2-yl)-ethanone	MS ES ⁺ m/e 343 (M-1).	

-43-

PREPARATION 72

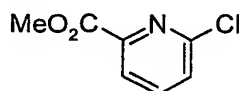
2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-boronic acid



- A solution of 3-bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (PREP.
5 17, 0.2 g, 0.69 mmol) in THF (10 mL) is cooled to -78°C and treated with tert-butyllithium (1.7 M in pentane, 1.6 mL, 2.8 mmol). This solution is stirred for 30 minutes at -78°C , treated with triisopropyl borate (0.39 g, 2.08 mmol), and stirred for 2 hr at -78°C . The reaction is then quenched with 1N HCl and stirred for 30 minutes at room temp. Evaporation leads to the solid crude product that is used without further
10 purification. MS ES⁺ m/e 253.9 (M+1).

PREPARATION 73

Methyl 6-chloropicolinate

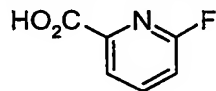


- 15 Add thionyl chloride (3.7 mL, 50.8 mmol) to a solution of 6-chloropicolinic acid (4.0 g, 25.4 mmol) in methanol (85mL) at 0°C . Stir the resultant solution for 15 minutes at 0°C , 0.5 hours at room temperature, and 6 hours at 50°C . Concentrate the reaction in vacuo and dilute with CHCl_3 (150mL). Wash the organic solution with saturated aqueous sodium bicarbonate (3 x 100mL), and brine (1 x 100mL) and dry with sodium sulfate.
20 Filtration and concentration afford methyl 6-chloropicolinate 4.38 g (100%) as a white solid.
 ^1H NMR (CDCl_3): δ 8.05 (m, 1H), 7.73 (m, 1H), 7.42 (m, 1H), 3.95 (s, 3H).

-44-

PREPARATION 74

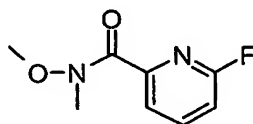
6-Fluoro-pyridine-2-carboxylic acid



- Add potassium permanganate (12.8 g, 81.0 mmol) to a solution of 2-fluoro-5-methylpyridine (3.0 g, 27.0 mmol) in water (135 mL). Heat the reaction to 100 °C for 4 hours. While the reaction is hot, filter through Celite®. Rinse the filter cake with hot water (2 x 50 mL) and concentrate the combined aqueous solutions in vacuo to a volume of 50 mL. Acidify with concentrated HCl and concentrate to dryness in vacuo to provide the title compound as a white solid which is used directly in the next step.
- MS APCI⁺ m/e 142 (M+1).

PREPARATION 75

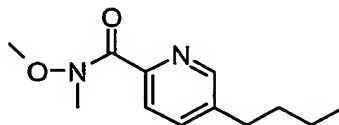
6-Fluoro-pyridine-2-carboxylic acid methoxy-methyl-amide



- Add N-methylmorpholine (6 mL, 52 mmol) and isobutylchloroformate (3.5 mL, 26.9 mmol) to a solution of 6-fluoropyridine-2-carboxylic acid (3.8 g, 26.9 mmol) in methylene chloride at 0°C. After 15 minutes add O,N-dimethylhydroxylamine hydrochloride (2.6 g, 26.9 mmol) and N-methylmorpholine (3 mL, 26.9 mmol). Stir the reaction at 0°C for 15 minutes and then room temperature for 17 hours. Dilute the reaction with methylene chloride and wash sequentially with water (1 x 50 mL), 10% aqueous citric acid (1 x 50 mL), brine (1 x 50 mL), saturated aqueous sodium bicarbonate (1 x 50 mL), and brine (1 x 50 mL). Dry the resulting organic solution with Na₂SO₄, filter, and purify by flash column chromatography (Silica Gel, 20% acetone/hexanes) to provide the title compound 0.97g (18% from 2-fluoro-5-methylpyridine) as a clear, yellow oil.
- MS APCI⁺ m/e 185 (M+1).
- TLC (SiO₂): R_f 0.40 (1:3 acetone/hexanes).

PREPARATION 76

5-Butyl-pyridine-2-carboxylic acid methoxy-methyl-amide

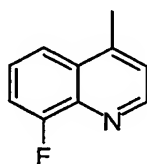


5 Add N-methylmorpholine (1.22 mL, 11.1 mmol) and isobutylchloroformate (1.44 mL, 11.1 mmol) to a solution of fusaric acid (2.0 g, 11.1 mmol) in methylene chloride at 0°C. After 15 minutes add O,N-dimethylhydroxylamine hydrochloride (1.1 g, 11.1 mmol) and N-methylmorpholine (1.22 mL, 11.1 mmol). Stir the reaction for at 0°C 15 minutes and then room temperature for 19 hours. Dilute the reaction with methylene chloride and wash with water (1 x 50 mL), 10% aqueous citric acid (1 x 50 mL), brine (1 x 50 mL), saturated aqueous sodium bicarbonate (1 x 50 mL), and brine (1 x 50 mL).
10 Dry the organic solution with sodium sulfate, filter, and concentrate in vacuo to provide the title compound 3.2 g (100%) as a clear yellow oil.
MS APCI⁺ m/e 201 (M+1).TLC (SiO₂): R_f 0.70 (1:1 ethyl acetate/methylene chloride).

15

PREPARATION 77

8-Fluoro-4-methyl-quinoline



Add H₂SO₄ (14.4 mL, 270 mmol) to a solution of 2-fluoroaniline (20.0 g, 180 mmol) in 1,4-dioxane (1L) at room temperature. Heat the mixture to reflux and add
20 methyl vinyl ketone (19.5 mL, 270 mmol) in 1,4-dioxane (50 mL) dropwise over 3 hours. Continue to heat for 1 hour after the addition, then remove the solvent under vacuum. Dissolve the residue in water (100 mL), neutralize with Na₂CO₃ and extract with CH₂Cl₂. Wash the combined organic extracts with water and brine, dry with anhydrous Na₂SO₄ and filter the mixture. Concentrate the filtrate; chromatograph the residue with silica gel
25 (elute with 20% EtOAc in hexanes) to give the title compound 12 g (41%) as a yellowish solid.

^1H NMR (CDCl_3) δ 8.80-8.75 (m, 1H), 7.85-7.80 (m, 3H), 7.60-7.30 (m, 3H), 3.70 (s, 3H).

5

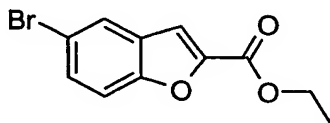
By the method of PREPARATION 77 the following compounds were prepared:

PREP. #	Product (Chemical Name)	Physical Data
78	6-Bromo-4-methyl-quinoline	^1H NMR (CDCl_3) δ 8.78-8.75 (m, 1H), 8.16-8.11 (m, 1H), 7.99-7.91 (m, 1H), 7.81-7.72 (m, 1H), 7.28-7.19 (m, 1H), 2.67 (s, 3H).
79	7-Trifluoromethyl-4-methyl-quinoline	^1H NMR (CDCl_3) δ 8.80-8.75 (m, 1H), 8.15-8.10 (m, 1H), 7.80 (s, 1H), 7.60-7.55 (m, 1H), 7.30-7.27 (m, 1H), 2.70 (s, 3H).
80	7-Bromo-4-methyl-quinoline	^1H NMR (CDCl_3) δ 8.80-8.75 (m, 1H), 8.30 (s, 1H), 7.90-7.85 (m, 1H), 7.70-7.65 (m, 1H), 7.25-7.20 (m, 1H), 2.65 (s, 3H).
81	4-Methyl-6-trifluoromethyl-quinoline	^1H NMR (CDCl_3) δ 8.91-8.86 (m, 1H), 8.32 (s, 1H), 8.27-8.19 (m, 1H), 7.91-7.86 (m, 1H), 7.39-7.32 (m, 1H), 2.69 (s, 3H).
82	7-Methoxy-4-methyl-quinoline	^1H NMR (CDCl_3) δ 8.71-8.66 (m, 1H), 7.91-7.87 (m, 1H), 7.44-7.40 (m, 1H), 7.28-7.18 (m, 1H), 7.11-7.06 (m, 1H), 3.95 (s, 3H), 2.67 (s, 3H).
83	7-Chloro-4-methyl-quinoline	
84	7-Ethoxy-4-methyl-quinoline	TOF MS ES^+ exact mass calculated for $\text{C}_{12}\text{H}_{14}\text{NO}$ (p+1): $m/z = 188.1075$ Found: 188.1059
85	6,7-di-Methoxy-4-methyl-quinoline	TOF MS ES^+ exact mass calculated for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ (p+1): $m/z = 204.1025$ Found: 204.1010
86	6,7-di-Chloro-4-methyl-quinoline	MS ES^+ m/e 212 (M+1)
87	6,7-di-Fluoro-4-methyl-quinoline	MS ES^+ m/e 212 (M+1)
88	6-Ethoxy-4-methyl-quinoline	TOF MS ES^+ exact mass calculated for $\text{C}_{12}\text{H}_{14}\text{NO}$ (p+1): $m/z = 188.1075$. Found: 188.1079

-47-

PREPARATION 89

5-Bromo-benzofuran-2-carboxylic acid ethyl ester

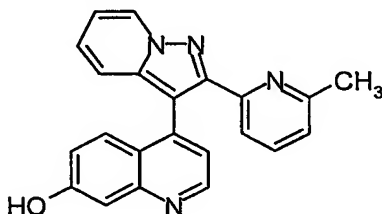


A solution of 5-bromo-salicylaldehyde (5.0 g, 25 mmol) and bromo
5 diethylmalonate (8.9 g, 37 mmol) in methyl ethyl ketone (50 mL) is treated with
potassium carbonate (6.8 g, 50 mmol) and heated to reflux. The reaction is stirred over 3
days at reflux. The reaction is then concentrated to a crude solid that is purified by silica
gel column chromatography (9:1 hexane / EtOAc) to afford 5.2 g (78%) of the desired
product. ¹H NMR (CDCl₃) 7.81 (d, 1H), 7.26-7.55 (m, 3H), 4.44 (q, 2H), 1.42 (t, 3H).

10

PREPARATION 90

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-ol



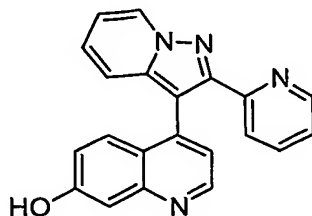
To a solution of 7-methoxy-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-
15 3-yl]-quinoline (1.3 g, 3.57 mmol) in DMF (36 mL), add ethanethiol (5.3 mL, 71.4
mmol), followed by sodium hydride (60% dispersion in mineral oil, 2.9 g, 71.4 mmol).
After all of the gas has evolved, the mixture is heated at 80 °C for 4 hours, then cooled to
room temperature. Saturated aqueous NH₄Cl (5 mL) is added, and the mixture
concentrated. The residue is dissolved in methylene chloride, washed with water and
20 concentrated to give the title compound 1.16g (93%) as a yellow solid.

¹H NMR (CD₃OD) δ 8.73-8.68 (m, 1H), 8.60-8.56 (m, 1H), 7.56-7.49 (m, 1H), 7.41-7.18
(m, 5H), 7.15-7.01 (m, 3H), 6.89-6.82 (m, 1H), 2.32 (s, 3H).

-48-

PREPARATION 91

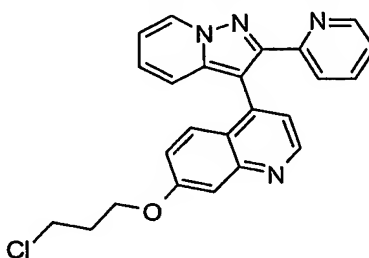
4-(2-Pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-ol



Add ethanethiol (6.8 mL, 92.5 mmol), followed by a sodium hydride (60% dispersion in mineral oil, 3.7 g, 92.5 mmol) to a solution of 7-methoxy-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline (1.63 g, 4.6 mmol) in DMF (50 mL) at room temperature. Following the same procedure described above affords the title compound 0.8g (52%) as a yellow solid.

PREPARATION 92

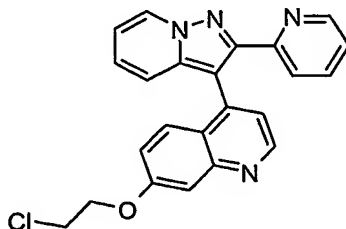
7-(3-Chloro-propoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline



4-(2-Pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-ol in a solution of DMF and MeOH is treated with 1-bromo-3-chloropropane (3 equiv) and cesium carbonate (2 equiv). The reaction is heated to 60 °C and stirred overnight. The reaction is then purified on silica gel column (see Prep. 77) chromatography to afford the desired product. MS ES⁺ m/e 415.0 (M+1).

PREPARATION 93

7-(2-Chloro-ethoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline

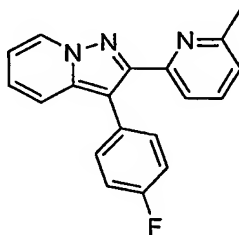


4-(2-Pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-ol in a solution of DMF and MeOH was treated with 1-bromo-2-chloroethane (3 equiv) and cesium carbonate (2 equiv). The reaction was heated to 60 °C and stirred overnight. As described above, the desired product was then obtained upon chromatographic purification (EtOAc, followed by MeOH, then 2 M NH₃ in MeOH). Yield; 30% overall from Prep. 90. MS ES⁺ m/e 401.0 (M+1).

10

EXAMPLE 1

3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine



A solution of 3-bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (0.25 g, 0.9 mmol) and p-fluorophenyl-boronic acid (0.15 g, 1.04 mmol), in DME (10 mL) is purged with argon. The solution is treated with NaOH (0.07 g, 1.7 mmol) and (PPh₃)₄Pd (0.05 g, 0.04 mmol) then heated at reflux overnight. The reaction is then cooled, diluted in EtOAc, and washed with water and brine. The organic solution is dried over MgSO₄ and the solvent removed in vacuo. The residue is purified by silica gel column chromatography using a mixture of hexanes/EtOAc to afford 0.164 g (62%) of desired product as a white solid. UV (95% EtOH) λ_{max} 248 nm (ϵ 20386). TOF MS ES⁺ exact mass calculated for C₁₉H₁₄FN₃ (p+1): m/z = 304.1250. Found: 304.1249. Anal. Calcd for C₁₉H₁₄FN₃: C, 75.23; H, 4.65; N, 13.85. Found: C, 75.10; H, 4.76; N, 13.70.

20

By the method of EXAMPLE 1 the following compounds were prepared:

EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
2	Dimethyl-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-phenyl}-amine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	4-(N,N-Dimethylamino)Phenyl boronic acid	TOF MS ES ⁺ exact mass calculated for C ₂₁ H ₁₂₀ N ₄ (p+1): m/z = 329.1766. Found: 329.1768.	
3	3-(4-Methoxy-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	p-methoxyphenylboronic acid	Anal. Calcd for C ₂₀ H ₁₇ N ₃ O: C, 76.17; H, 5.43; N, 13.32. Found: C, 75.84; H, 5.42; N, 13.07.	
4	3-(4-Methanesulfonyl-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	4-(Methanesulfonyl)benzeneboronic acid	TOF MS ES ⁺ exact mass calculated for C ₂₀ H ₁₈ N ₃ O ₂ S (p+1): m/z = 364.1120. Found: 364.1134	
5	2-(6-Methyl-pyridin-2-yl)-3-phenyl-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	Phenylboronic acid	Anal. Calcd for C ₁₉ H ₁₅ N ₃ : C, 79.98; H, 5.30; N, 14.73.	Use 5:1 Toluene: MeOH instead of DME as solvent.

EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
				Found: C, 79.94; H, 5.40; N, 14.59.	Use Na ₂ CO ₃ instead of NaOH.
6	2-(6-Methyl- pyridin-2-yl)-3- pyridin-4-yl- pyrazolo[1,5- a]pyridine	3-Bromo-2-(6- methyl-pyridin- 2-yl)- pyrazolo[1,5- a]pyridine (Prep. 17)	Pyridine-4-boronic acid	MS ES ⁺ m/e 287.2 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
7	3-(4-Fluoro- phenyl)-2-(6- methyl-pyridin-2- yl)-6-phenyl- pyrazolo[1,5- a]pyridine	3-Bromo-2-(6- methyl- pyridin-2-yl)- 6-phenyl- pyrazolo[1,5- a]pyridine (Prep. 18)	p-Fluorophenylboronic acid	MS ES ⁺ m/e 380.2 (M+1).	Use 5:1 Toluene:Me OH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
8	3-(4-Fluoro- phenyl)-6- methanesulfonyl-2- (6-methyl-pyridin- 2-yl)-pyrazolo[1,5- a]pyridine	3-Bromo-6- methanesulfon yl-2-(6-methyl- pyridin-2-yl)- pyrazolo[1,5- a]pyridine (Prep. 20)	p-Fluorophenylboronic acid	MS ES ⁺ m/e 382.1 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
9	2-(6-Methyl- pyridin-2-yl)-3-(4- trifluoromethyl- phenyl)- pyrazolo[1,5- a]pyridine	3-Bromo-2-(6- methyl- pyridin-2-yl)- pyrazolo[1,5- a]pyridine (Prep. 17)	4- Trifluoromethylphenylb oronic acid	MS ES ⁺ m/e 354.0 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.

EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
10	3-(6-Methoxy-pyridin-3-yl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	2-Methoxy-5-Pyridineboronic acid	TOF MS ES ⁺ exact mass calculated for C ₁₉ H ₁₆ N ₄ O (p+1): m/z = 317.1402. Found: 317.1416.	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
11	3-Benzo[1,3]dioxol-yl-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	3,4-Methylenedioxybenzeneboronic acid	TOF MS ES ⁺ exact mass calculated for C ₂₀ H ₁₅ N ₃ O ₂ (p+1): m/z = 330.1243. Found: 330.1243.	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
12	3-(3,5-Difluorophenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	3,5-Difluorophenylboronic acid	TOF MS ES ⁺ exact mass calculated for C ₁₉ H ₁₃ F ₂ N ₃ (p+1): m/z = 322.1156. Found: 322.1147.	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
13	2-(6-Methyl-pyridin-2-yl)-3-p-tolyl-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	p-Tolylboronic acid	TOF MS ES ⁺ exact mass calculated for C ₂₀ H ₁₇ N ₃ (p+1): m/z = 300.1501. Found: 300.1522	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.

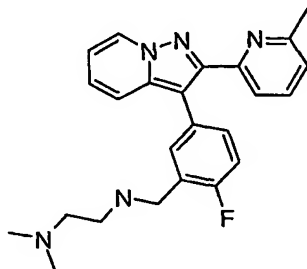
EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
14	3-(1H-Indol-5-yl)- 2-(6-methyl- pyridin-2-yl)- pyrazolo[1,5- a]pyridine	3-Bromo-2-(6- methyl- pyridin-2-yl)- pyrazolo[1,5- a]pyridine (Prep. 17)	5-Indolylboronic acid	TOF MS ES ⁺ exact mass calculated for C ₂₁ H ₁₆ N ₄ (p+1): m/z = 325.1453. Found: 325.1465	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
15	3-[2-(6-Methyl- pyridin-2-yl)- pyrazolo[1,5- a]pyridin-3-yl]- benzamide	3-Bromo-2-(6- methyl- pyridin-2-yl)- pyrazolo[1,5- a]pyridine (Prep. 17)	Benzamide-3-boronic acid	MS ES ⁺ m/e 329.1 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
16	3-(3,4-Dimethoxy- phenyl)-2-(6- methyl-pyridin-2- yl)-pyrazolo[1,5- a]pyridine	3-Bromo-2-(6- methyl- pyridin-2-yl)- pyrazolo[1,5- a]pyridine (Prep. 17)	3,4- Dimethoxyphenylboron ic acid	MS ES ⁺ m/e 346.2 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
17	N,N-Dimethyl-3-[2- (6-methyl-pyridin- 2-yl)-pyrazolo[1,5- a]pyridin-3-yl]- benzamide	PREP. 17	N,N- Dimethylbenzamide-3- boronic acid	MS ES ⁺ m/e 357.2 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
18	2-Fluoro-5-[2-(6- methyl-pyridin-2- yl)-pyrazolo[1,5-	PREP. 17	4-Fluoro-3- formylbenzene boronic acid	TOF MS ES ⁺ exact	Use 5:1 Toluene: MeOH

EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
	4-[pyridin-3-yl]-benzaldehyde			mass calculated for $C_{12}H_{14}NO$ (p+1):m/z = 332.1199. Found: 332.1211	instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
19	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-phenylamine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl) aniline	MS ES ⁺ m/e 301.1 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
20	N-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-phenyl}-acetamide	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl) acetamide	MS ES ⁺ m/e 343.1 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
21	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-phenol	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl) phenol	MS ES ⁺ m/e 302.0 (M+1).	Use 5:1 Toluene: MeOH instead of DME as solvent. Use Na ₂ CO ₃ instead of NaOH.
22	3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	1,4-Benzodioxane-6-boronic acid	TOF MS ES ⁺ exact mass calculated	Use 5:1 Toluene: MeOH instead of DME as

EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
	a]pyridine	(Prep. 17)		for $C_{21}H_{18}N_3O_2$ (p+1): m/z = 344.1399. Found: 344.1412.	solvent. Use Na ₂ CO ₃ instead of NaOH.
23	3-(3-Methoxy-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	3-Methoxyphenyl boronic acid	MS ES ⁺ m/e 316.0 (M+1).	
24	3-(3-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 17)	3-Fluorophenylboronic acid	MS ES ⁺ m/e 304.0 (M+1).	
25	2-(6-Ethyl-pyridin-2-yl)-3-(4-methoxy-phenyl)-pyrazolo[1,5-a]pyridine	3-Bromo-2-(6-ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 22)	4-Methoxyphenylboronic acid	TOF MS ES ⁺ exact mass calculated for $C_{21}H_{19}N_3$ O (p+1): m/z = 330.1606. Found: 330.1602	
26	4-[2-(6-Ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-phenol	(6-ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (Prep. 22)	4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl) phenol	TOF MS ES ⁺ exact mass calculated for $C_{20}H_{17}N_3$ O (p+1): m/z = 316.1450. Found: 316.1435.	

EXAMPLE 27

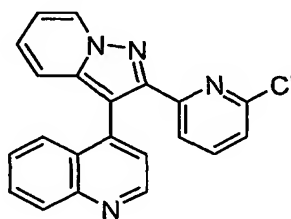
N'-{2-Fluoro-5-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-benzyl}-N,N-
dimethyl-ethane-1,2-diamine



5 A solution of 2-fluoro-5-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-benzaldehyde (0.05 g, 0.15 mmol), N,N-dimethyl-ethylenediamine (0.013 g, 0.15 mmol), trimethyl orthoformate (2 mL) in MeOH (5 mL) is stirred for 2 hours at room temperature. The reaction is then treated with sodium borohydride (6.8 mg, 0.18 mmol) and stirred overnight. The reaction is then quenched with 2N NaOH and stirred for 30
10 minutes. The solution is diluted in CH₂Cl₂ and washed with saturated aqueous NaHCO₃, brine, and dried over sodium sulfate. The solvent is removed in vacuo to afford 0.06 g (100%) of desired product. MS ES⁺ m/e 404.1 (M+1).

EXAMPLES 28

15 4-[2-(6-Chloro-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline



Add 1-aminopyridinium iodide (780 mg, 3.53 mmol), N,N-diisopropylethylamine (0.62 mL, 3.53 mmol), 1-(6-chloro-pyridin-2-yl)-2-quinolin-4-yl-ethanone (500 mg, 1.77 mmol), and ethanol (8 mL) to a sealed tube apparatus. The sealed vessel is heated at
20 110°C for 5 hours. After cooling, the crude is concentrated in vacuo. Purification by flash column chromatography (Silica Gel, 25-40% acetone/hexanes) provides the title compound 119 mg (19%) as an orange solid.
MS APCI⁺ m/e 357 (M+1).

By the method of EXAMPLE 28 the following compounds were prepared:

EX. #	Product Name	Physical Data	Pyridinium Salt
29	3-(4-Fluoro-phenyl)-2-pyridin-2-yl-pyrazolo[1,5-a]pyridine	MS ES ⁺ m/e 290 (M+1).	1-Amino-pyridinium; iodide
30	7-Ethoxy-4-(4-phenyl-2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	MS ES ⁺ m/e 443 (M+1).	1-Amino-3-phenyl-pyridinium; 2,4,6-trimethyl-benzenesulfonate
31	7-Ethoxy-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	MS ES ⁺ m/e 367 (M+1).	1-Amino-pyridinium; iodide
32	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₂ H ₁₇ N ₄ (p+1): m/z = 337.1453. Found: 337.	1-Amino-pyridinium; iodide
33	7-Ethoxy-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₄ H ₂₁ N ₄ O (p+1): m/z = 381.1715. Found: 381.1722	1-Amino-pyridinium; iodide
34	4-[2-(6-Ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₃ H ₁₉ N ₄ (p+1): m/z = 351.1610. Found: 351.1628	1-Amino-pyridinium; iodide
35	6,7-Dimethoxy-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₄ H ₂₁ N ₄ O ₂ (p+1): m/z = 397.1665. Found: 397.1665	1-Amino-pyridinium; iodide
36	7-Chloro-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS ES ⁺ m/e 371 (M+1).	1-Amino-pyridinium; iodide
37	6-Ethoxy-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS ES ⁺ m/e 381 (M+1).	1-Amino-pyridinium; iodide
38	3-(4-Fluoro-naphthalen-1-yl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	MS ES ⁺ m/e 354 (M+1).	1-Amino-pyridinium; iodide
39	4-(2-Furan-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₀ H ₁₄ N ₃ O (p+1): m/z	1-Amino-pyridinium; iodide

EX. #	Product Name	Physical Data	Pyridinium Salt
		= 312.1137. Found: 312.1126	
40	4-(2-Thiophen-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₀ H ₁₄ N ₃ S (p+1): m/z = 328.0908. Found: 328.0914	1-Amino-pyridinium; iodide
41	7-Methoxy-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS ES ⁺ m/e 367 (M+1).	1-Amino-pyridinium; iodide
42	6,7-Difluoro-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS ES ⁺ m/e 373 (M+1).	1-Amino-pyridinium; iodide
43	6,7-Dichloro-4-[2-(6-ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS ES ⁺ m/e 419 (M+1).	1-Amino-pyridinium; iodide
44	4-[2-(6-Ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-6,7-dimethoxy-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₅ H ₂₃ N ₄ O ₂ (p+1): m/z = 411.1821. Found: 411.1828	1-Amino-pyridinium; iodide
45	6,7-Dichloro-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS ES ⁺ m/e 405.0 (M+1).	1-Amino-pyridinium; iodide
46	7-Ethoxy-4-[2-(6-ethyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	TOF MS ES ⁺ exact mass calculated for C ₂₅ H ₂₃ N ₄ O (p+1): m/z = 395.1872. Found: 394.1794	1-Amino-pyridinium; iodide
47	2-(6-Ethyl-pyridin-2-yl)-3-(4-fluoro-naphthalen-1-yl)-pyrazolo[1,5-a]pyridine	TOF MS ES ⁺ exact mass calculated for C ₂₄ H ₁₉ FN ₃ (p+1): m/z = 368.1563. Found: 368.1569	1-Amino-pyridinium; iodide
48	3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-6-carboxylic acid ethyl ester	TOF MS ES ⁺ exact mass calculated for C ₂₂ H ₁₉ FN ₃ O ₂ (p+1): m/z = 376.1461. Found: 376.1457	1-Amino-3-methoxycarbonyl-pyridinium; 2,4,6-trimethyl-benzenesulfonate

EX. #	Product Name	Physical Data	Pyridinium Salt
49	3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-4-carboxylic acid ethyl ester	TOF MS ES ⁺ exact mass calculated for C ₂₂ H ₁₉ FN ₃ O ₂ (p+1): m/z = 376.1461. Found: 376.1464	1-Amino-3-methoxycarbonyl-pyridinium; 2,4,6-trimethyl-benzenesulfonate
50	3-(4-Fluoro-phenyl)-4-iodo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	TOF MS ES ⁺ exact mass calculated for C ₁₉ H ₁₄ FIN ₃ (p+1): m/z = 430.0216. Found: 430.0241	1-Amino-3-iodo-pyridinium; 2,4,6-trimethyl-benzenesulfonate
51	3-(4-Fluoro-phenyl)-2-(6-propyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	TOF MS ES ⁺ exact mass calculated for C ₂₁ H ₁₉ FN ₃ (p+1): m/z = 332.1563. Found: 332.1563	1-Amino-pyridinium; iodide
52	2-(6-Ethyl-pyridin-2-yl)-3-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyridine	TOF MS ES ⁺ exact mass calculated for C ₂₀ H ₁₇ FN ₃ (p+1): m/z = 318.1406. Found: 318.1404	1-Amino-pyridinium; iodide
53	3-Pyridin-4-yl-2-pyridin-2-yl-pyrazolo[1,5-a]pyridine	MS ES ⁺ m/e 273.3 (M+1).	1-Amino-pyridinium; iodide
54	4-(2-Pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	MS ES ⁺ m/e 323 (M+1).	1-aminopyridinium iodide
55	4-[2-(6-Fluoro-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS APCI ⁺ m/e 340 (M+1).	1-aminopyridinium iodide
56	4-[2-(5-Butyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS APCI ⁺ m/e 379 (M+1).	1-aminopyridinium iodide
57	8-Fluoro-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS APCI ⁺ m/e 355 (M+1).	1-aminopyridinium iodide
58	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-6-trifluoromethyl-quinoline	MS APCI ⁺ m/e 405 (M+1).	1-aminopyridinium iodide
59	7-Bromo-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS APCI ⁺ m/e 415, 417 (M+1).	1-aminopyridinium iodide
60	4-[2-(6-Methyl-pyridin-2-	MS APCI ⁺ m/e 405	1-aminopyridinium

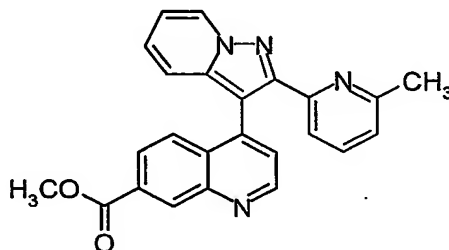
EX. #	Product Name	Physical Data	Pyridinium Salt
	yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-trifluoromethyl-quinoline	(M+1).	iodide
61	3-(3-Chloro-4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	MS APCI ⁺ m/e 338 (M+1).	1-aminopyridinium iodide
62	2-(6-Methyl-pyridin-2-yl)-3-(2,4,5-trifluoro-phenyl)-pyrazolo[1,5-a]pyridine	MS APCI ⁺ m/e 340 (M+1).	1-aminopyridinium iodide
63	3-(4-Fluoro-3-trifluoromethyl-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	MS APCI ⁺ m/e 372 (M+1).	1-aminopyridinium iodide
64	2-(6-Chloro-pyridin-2-yl)-3-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyridine	MS APCI ⁺ m/e 324 (M+1).	1-aminopyridinium iodide
65	4-[2-(5-Bromo-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS APCI ⁺ m/e 401 (M+1).	1-aminopyridinium iodide
66	4-(5-Benzyl-2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	MS APCI ⁺ m/e 413 (M+1).	4-Benzyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate
67	4-[5-Benzyl-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-bromo-quinoline	MS APCI ⁺ m/e 505 (M+1).	4-Benzyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate
68	4-(5-Benzyl-2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-7-bromo-quinoline	MS APCI ⁺ m/e 491 (M+1).	4-Benzyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate
69	2-Pyridin-2-yl-3-quinolin-4-yl-pyrazolo[1,5-a]pyridine-5-carboxylic acid ethyl ester	MS APCI ⁺ m/e 395 (M+1).	4-Methoxycarbonyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate
70	2-(Pyridin-2-yl)-3-(quinolin-4-yl)-pyrazolo[1,5-a]pyridine-6-carboxylic acid ethyl ester	MS APCI ⁺ m/e 395 (M+1).	3-Ethoxycarbonyl-pyridin-1-yl-ammonium 2,4,6-trimethyl-benzenesulfonate
71	7-Methoxy-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	¹ H NMR (CDCl ₃) δ 8.87-8.84 (m, 1H), 8.69-8.63 (m, 1H), 7.58-7.53 (m, 1H), 7.51-7.48 (m, 1H), 7.37-7.06 (m, 5H),	1-aminopyridinium iodide

-61-

EX. #	Product Name	Physical Data	Pyridinium Salt
		7.02-6.95 (m, 2H), 6.92-6.85 (m, 1H), 3.50 (s, 3H), 2.44 (s, 3H).	
72	7-Methoxy-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	MS APCI ⁺ m/e 353 (M+1).	1-aminopyridinium iodide

EXAMPLE 73

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid methyl ester



5

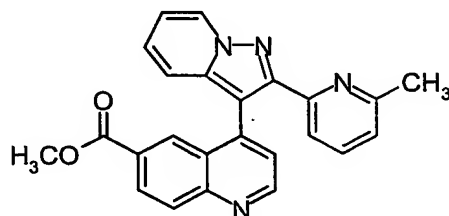
Combine 7-bromo-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline (0.18 g, 0.43 mmol), triphenylphosphine (36 mg, 0.14 mmol), sodium acetate (0.05 g, 0.61 mmol), methanol (2.7 mL), and DMF (2.7 mL). Bubble nitrogen gas through the solution for 10 minutes. Add palladium acetate (0.03 g, 0.13 mmol). Bubble nitrogen gas through the solution for another 10 minutes. Connect a carbon monoxide balloon to the reaction vessel and heat at 80 °C for 24 hours. Evaporate the solvent in vacuo. Chromatograph the residue on silica gel (elute with 50% ethyl acetate/hexanes then 75% ethyl acetate/hexanes) to afford the title compound 72 mg (42%) as a yellowish solid.

15 MS APCI⁺ m/e 395 (M+1).

-62-

EXAMPLE 74

4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-6-carboxylic acid methyl ester

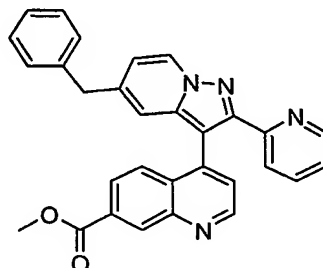


5 Using a method similar to EXAMPLE 73, using 6-bromo-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline (0.14 g, 0.35 mmol) affords the title compound 0.11 g (82%) as a yellowish solid.
MS APCI⁺ m/e 395 (M+1).

10

EXAMPLE 75

4-(5-Benzyl-2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline-7-carboxylic acid methyl ester



To a solution of 4-(5-benzyl-2-pyridin-2-yl-pyrazolo-[1,5-a]pyridin-3-yl)-7-bromo-quinoline (118 mg, 0.24 mmol) in DMF (4 mL) and methanol (4 mL), add triphenylphosphine (20 mg, 0.07 mmol) and sodium acetate (28 mg, 0.36 mmol). Bubble nitrogen for 10 minutes. Add palladium acetate (16 mg, 0.07 mmol) and bubble nitrogen for another 10 minutes. Bubble carbon monoxide through the solution for 5 minutes and attach a carbon monoxide balloon. Heat the reaction mixture at 80 °C for 2 days. Cool the reaction mixture to room temperature. Add water (20 mL) and extract the aqueous solution with ethyl acetate (3 x 20 mL). Dry the combined organic layers with sodium sulfate and concentrate. Purify by flash

column chromatography (SiO₂, 20-50% ethyl acetate/hexanes) to give the title compound 84 mg (75%) as a yellow solid.

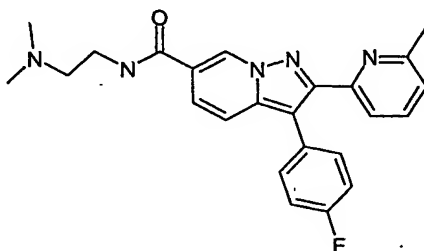
MS APCI⁺ m/e 471 (M+1).

TLC (SiO₂): R_f 0.25 (30% ethyl acetate/ hexanes)

5

EXAMPLE 76

3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-6-carboxylic acid (2-dimethylamino-ethyl)-amide



- 10 Heat 3-(4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-6-carboxylic acid ethyl ester (75 mg , 0.2 mmol) in 2 ml of N,N-dimethylethylenediamine at 90 °C for 6 hr in a sealed glass tube with stirring. Extract reaction solution once with water/methylene chloride and concentrate the organic layer in vacuo. Purify using preparative TLC (Silica Gel, 90:10 methylene chloride/methanol) to give 12 mg (10%) of
- 15 the title compound MS ES⁺ m/e 418.2 (M+1).

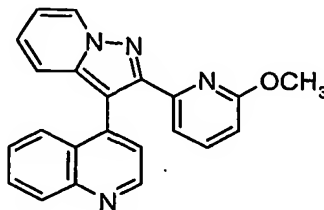
By the method of EXAMPLE 76 the following compounds were prepared:

EX. #	Product Name	Physical Data
77	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-6-carboxylic acid (2-dimethylamino-ethyl)-amide	MS APCI ⁺ m/e 451 (M+1).
78	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (2-dimethylamino-ethyl)-amide	MS APCI ⁺ m/e 451 (M+1).
79	5-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-benzofuran-2-carboxylic acid (2-dimethyl amino-ethyl)-amide	TOF MS ES ⁺ exact mass calculated for C ₂₆ H ₂₆ N ₅ O ₂ (p+1): m/z = 440.2086. Found: 440.2110.
80	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide	MS APCI ⁺ m/e 520 (M+1).

-64-

EXAMPLE 81

4-[2-(6-Methoxy-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline

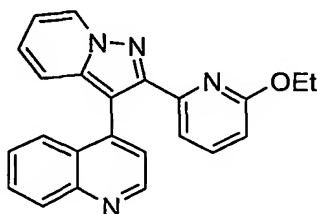


Add methanol (19 mg, 0.59 mmol) and sodium hydride (14 mg, 60% dispersion, 0.35 mmol) to a solution of 4-[2-(6-chloro-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline (42 mg, 0.118 mmol) in DMF (0.6 mL) at room temperature. Heat to 110 °C for 3 hours, cool to room temperature, and quench with saturated aqueous ammonium chloride (0.5 mL). Concentrate in vacuo, filter, and purify by flash column chromatography (Silica Gel, 20-40% acetone/hexanes) to provide the title compound 30 mg (73%) as a white solid.

MS APCI⁺ m/e 353 (M+1). TLC (SiO₂): R_f 0.20 (1:1 acetone/hexanes)

EXAMPLE 82

4-[2-(6-Ethoxy-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline



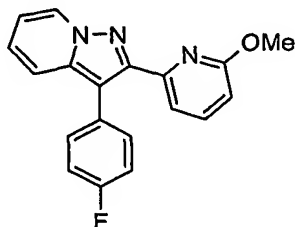
Add sodium hydride (25.5 mg, 0.64 mmol) to a solution of 4-[2-(6-chloro-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline (50 mg, 0.14 mmol) in ethanol (2.5 mL) at 0 °C. Stir the reaction mixture at 0 °C for 10 minutes, room temperature for 10 minutes more, and reflux overnight. Cool the reaction mixture to room temperature, quench with saturated aqueous ammonium chloride (3 mL). Add water (20 mL) and extract the aqueous solution with methylene chloride (3 x 20 mL). Dry the combined organic layers with sodium sulfate and purify by flash column chromatography (SiO₂, 50% ethyl acetate/hexanes) to give the title compound 48 mg (94%) as an off-white solid.

MS APCI⁺ m/e 367 (M+1).

-65-

EXAMPLE 83

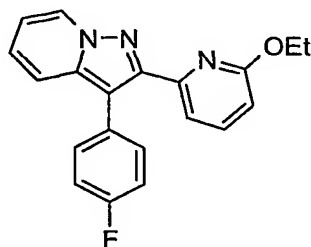
3-(4-Fluoro-phenyl)-2-(6-methoxy-pyridin-2-yl)-pyrazolo[1,5-a]pyridine



Add sodium hydride (20.7 mg, 60% dispersion in mineral oil, 0.52 mmol) to a solution of 2-(6-chloro-pyridin-2-yl)-3-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyridine (33.5 mg, 0.10 mmol) in DMF (2.5 mL) and methanol (2.5 mL) at room temperature. Stir the reaction mixture at room temperature for 4 hours and at 80 °C for 48 hours. Cool to room temperature and concentrate in vacuo. Add water (20 mL) and extract the aqueous solution with methylene chloride (3 x 20 mL). Dry the combined organic layers with sodium sulfate and concentrate. Purify by flash column chromatography (SiO₂, 50% ethyl acetate/hexanes) to give the title compound 31 mg (97%) as an off-white solid. MS APCI⁺ m/e 320 (M+1).

EXAMPLE 84

2-(6-Ethoxy-pyridin-2-yl)-3-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyridine

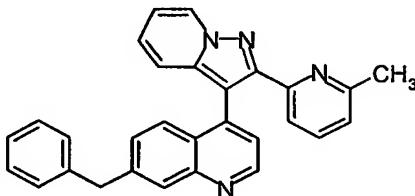


Add sodium hydride (20.7 mg, 0.52 mmol) to a solution of 2-(6-chloro-pyridin-2-yl)-3-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyridine (33.5 mg, 0.10 mmol) in ethanol (2.5 mL) at 0 °C. Stir the reaction mixture at 0 °C for 30 minutes and at 80 °C for 48 hours. Cool the reaction mixture to room temperature and concentrate in vacuo. Using the same procedure as above afforded the title compound 31 mg (93%) as an off-white solid. MS APCI⁺ m/e 334 (M+1).

-66-

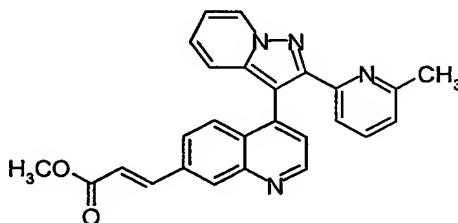
EXAMPLE 85

7-Benzyl-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline



Bubble nitrogen gas through 1 mL of THF for 10 minutes. Add benzyl
5 magnesium chloride (2M in THF, 0.12 mL, 0.24 mmol), zinc chloride (1M in diethyl
ether, 0.26 mL, 0.26 mmol). Bubble with nitrogen gas for 15 minutes. Add Pd(PPh₃)₂Cl₂
(4 mg, 0.006 mmol), 7-bromo-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-
quinoline (0.05 g, 0.12 mmol). Stir at room temperature for 48 hours. Quench with
aqueous saturated NH₄Cl solution. Evaporate the solvent in vacuo. Add methylene
10 chloride. Filter the mixture and concentrate the filtrate in vacuo. Chromatograph the
residue on silica gel (elute with 50% ethyl acetate/hexanes then 100% ethyl acetate).
Final purification by preparative HPLC affords the title compound 20 mg (40%) as a
yellow foam.
MS APCI⁺ m/e 427 (M+1).

15

EXAMPLE 863-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-
acrylic acid methyl ester

Combine 7-bromo-4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-
20 quinoline (0.15 g, 0.36 mmol), tri-*o*-tolylphosphine (0.38 g, 1.26 mmol), tributylamine
(0.12 mL, 0.5 mmol), methyl acrylate (0.065 mL, 0.72 mmol), anhydrous toluene (3 mL),
and DMF (1.5 mL). Bubble nitrogen gas through the solution for 20 minutes. Add
palladium acetate (4.0 mg, 0.018 mmol). Heat the reaction mixture at 80 °C for 48 hours.
25 Chromatograph the residue on silica gel (elute with 2% methanol/methylene chloride,

-67-

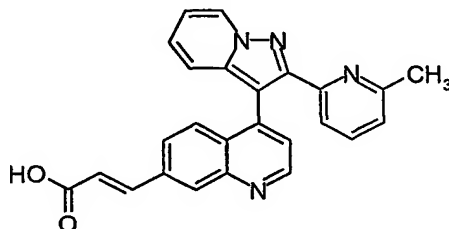
then 4% methanol/methylene chloride). Further purification by preparative HPLC affords the title compound 42 mg (28%) as a yellowish solid.

MS APCI⁺ m/e 421 (M+1).

5

EXAMPLE 87

3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-acrylic acid



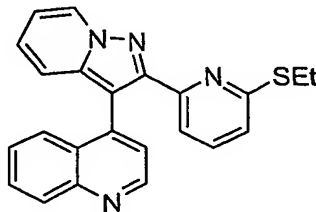
To a solution of 3-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-acrylic methyl ester (0.03 g, 0.07 mmol), THF (1mL), and H₂O (0.5 mL), add LiOH (0.012 g, 0.29 mmol). Stir the reaction mixture at room temperature for 24 hours. Evaporate the solvents in vacuo. Chromatograph the residue on SCX ion-exchange resin (elute with 95% methanol/ethyl acetate, then 100% methanol, then 2M NH₃ in methanol) to afford the title compound 26 mg (93%) as a yellowish solid.

MS APCI⁺ m/e 407 (M+1).

15

EXAMPLE 88

4-[2-(6-Ethylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline



20

Add ethanethiol (0.71 mL, 0.96 mmol) to a solution of 4-[2-(6-chloro-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline (37 mg, 0.1 mmol) in DMF (2.5 mL) at 0 °C. Add sodium hydride (38 mg, 0.96 mmol), stir the mixture at room temperature for 72 hours. Dilute the reaction mixture with methylene chloride (50 mL) and wash with water (2 x 50 mL), brine (1 x 50 mL). Dry the combined organic layers with sodium sulfate and

-68-

concentrate. Purify the residue by flash column chromatography (SiO₂, 50% ethyl acetate/hexanes) to give the title compound 35 mg (91%) as an off-white solid.

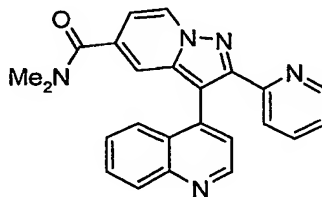
MS APCI⁺ m/e 383 (M+1).

5 By the method of EXAMPLE 88 the following compounds were prepared:

EX. #	Product Name	Physical Data
89	4-[2-(6-Phenylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS APCI ⁺ m/e 431 (M+1).
90	4-[2-(6-Morpholin-4-yl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline	MS APCI ⁺ m/e 408 (M+1).
91	3-(4-Fluoro-phenyl)-2-(6-methylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	MS APCI ⁺ m/e 336 (M+1).
92	3-(4-Methylsulfanyl-phenyl)-2-(6-methylsulfanyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine	MS APCI ⁺ m/e 364 (M+1).
93	Dimethyl-(2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-ylsulfanyl}-ethyl)-amine	MS ES ⁺ m/e 440 (M+1).

EXAMPLE 94

2-(Pyridin-2-yl)-3-(quinolin-4-yl)-pyrazolo[1,5-a]pyridine-5-carboxylic acid dimethylamide



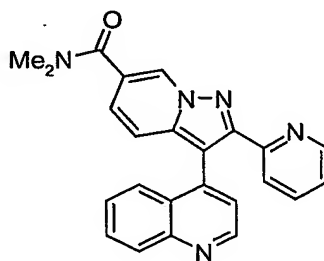
Add trimethylaluminum (0.54 mL, 1.08 mmol) dropwise to a solution of dimethylamine (0.45 mL, 0.90 mmol) in methylene chloride (1 mL) at 0 °C. Warm to room temperature and stir for 1 hour. Add 2-pyridin-2-yl-3-quinolin-4-yl-pyrazolo[1,5-a]pyridine-5-carboxylic acid ethyl ester (177 mg, 0.45 mmol) in methylene chloride (4 mL), and stir at room temperature for 1 hour and at 80 °C for 24 hours. Cool the reaction

-69-

mixture to room temperature. Add aqueous solution of potassium sodium tartarate (20 mL) and stir the solution for 1 hour. Separate the organic layers and extract the aqueous solution with methylene chloride (2 x 20 mL). Dry the combined organic layers with sodium sulfate and concentrate. Purify by flash column chromatography (SiO₂, 20-30% methanol/ methylene chloride) to give the title compound 54 mg (31%) as a yellow solid.
MS APCI⁺ m/e 394 (M+1).

EXAMPLE 95

2-(Pyridin-2-yl)-3-(quinolin-4-yl)-pyrazolo[1,5-a]pyridine-6-carboxylic acid dimethylamide

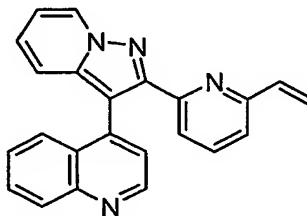


In the same manner as in the previous example 2-pyridin-2-yl-3-quinolin-4-yl-pyrazolo[1,5-a]pyridine-6-carboxylic acid ethyl ester (160 mg, 0.4 mmol) afforded the title compound 21 mg (13%) as a brownish-yellow foam.

MS APCI⁺ m/e 394 (M+1).

EXAMPLE 96

4-[2-(6-Vinyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline



Add tributylvinylstanane (0.056 mL, 0.182 mmol) to a solution of 4-[2-(6-chloro-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline (59 mg, 0.165 mmol) in toluene (0.83 mL) at room temperature and bubble nitrogen through the solution for 5 minutes. Add tetrakis(triphenylphosphine) palladium(0) (9 mg, 0.008 mmol) and bubble nitrogen through the solution for 1 minute. Heat the reaction to 110 °C for 15 hours. Purify by

-70-

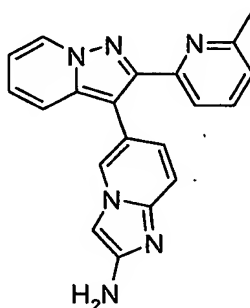
flash column chromatography (Silica Gel, 20-40% acetone/hexanes) to provide the title compound 11.5 mg (20%) as a white solid.

MS APCI⁺ m/e 349 (M+1).

5

EXAMPLE 97

6-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-imidazo[1,2-a]pyridin-2-ylamine



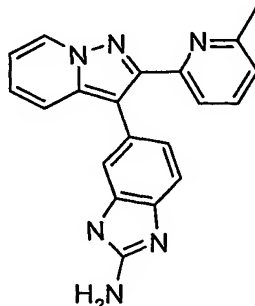
10 Stir 3-bromo-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine (500 mg, 1.74 mmol) in THF (20 ml) at -60 °C and add t-butyl lithium (4 ml, 6.94 mmol, 1.7M in pentane). Stir for 1 hour, then add tri-isopropyl borate (1.2 ml, 5.2 mmol) and warm to 0 °C for 1 hour. Quench with 1M HCl (5 ml). Concentrate in vacuo and redissolve in a 2:1 toluene/methanol mixture (30 ml). Adjust to pH 8 with aqueous 2M Na₂CO₃. Add 100 mg Pd(PPh₃)₄ and 2,2,2-trifluoro-N-(6-iodo-imidazo[1,2-a]pyridin-2-yl)-acetamide (200 mg, 15 563 mmol) and heat to 90 °C for 18 hours. Acidify with 1M HCl and extract with ethyl acetate (3 x 100 ml). Neutralize aqueous layer with 5N NaOH and extract with ethyl acetate (3 x 100 ml). Concentrate organic layer in vacuo and purify on Silica gel (eluting with 70/30 Hexane/ EtOAc). MS ES⁺ m/e 341.1 (M+1).

20

-71-

EXAMPLE 98

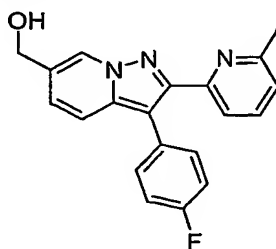
6-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-1H-benzimidazol-2-ylamine



A solution of 2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-boronic acid
 5 (0.5 g, crude) and 6-iodo-1-[(1-methylethyl)sulfonyl]-1H-benzimidazol-2-amine (0.2 g,
 1.04 mmol) in toluene (20 mL) and MeOH (4 mL) is treated with Na₂CO₃ (1.0M
 aqueous, 10 mL) and (PPh₃)₄Pd (100 mg) and then heated to reflux overnight. The
 reaction mixture is then cooled, diluted in EtOAc, and the organic phase is washed with
 water and then brine. The organic solution is dried over MgSO₄, filtered, and the solvent
 10 removed in vacuo. The residue is purified by silica gel column chromatography to afford
 0.026 g of 6-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-1-(propane-2-
 sulfonyl)-1H-benzimidazol-2-ylamine MS ES⁺ m/e 447.1 (M+1). This material (13 mg,
 0.029 mmol) is desulfonylated by heating in 1:1 acetonitrile:0.5 NaOH (10 ml) at 60 °C
 for 30 minutes. Dilution with water and extraction with methylene chloride (3 x 20 ml),
 15 followed by concentration of the organic layer in vacuo. Provides the desired product: MS
 ES⁺ m/e 341.0 (M+1).

EXAMPLE 99

[3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-6-yl]-methanol



20

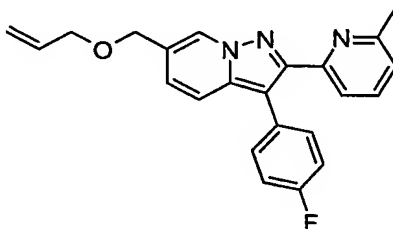
Stir EXAMPLE 49 (150 mg, 0.4 mmol) in ether at room temperature Add lithium
 aluminum hydride (100 mg) slowly and stir for 1 hour. Quench with EtOAc (10 ml) and

-72-

filter. Concentrate filtrate in vacuo and purify on silica gel (eluted with 90/10 methylene chloride). MS ES⁺ m/e 334.1 (M+1).

EXAMPLE 100

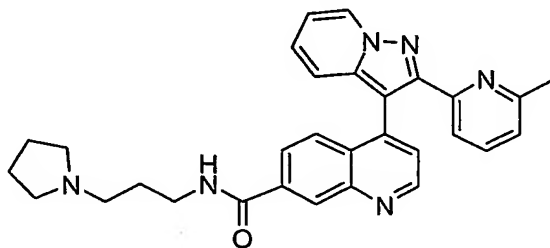
5 6-Allyloxymethyl-3-(4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine



A solution of EXAMPLE 99 (0.13 g, 0.39 mmol) and 1-bromo-3-chloropropane (0.06 g, 0.39 mmol) in DMF (10 mL) was treated with cesium carbonate (0.14 g, 0.43 mmol) and heated to 80 °C. The reaction is stirred overnight and is diluted with EtOAc and water. The organic phase is separated and washed with brine. After drying over Na₂SO₄, the organic phase is filtered, and the solvent removed to afford 0.04 g (27%) of product. MS ES⁺ m/e 374.0 (M+1).

EXAMPLE 101

15 4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide



Dissolve EXAMPLE 75 (0.065 g, 0.16 mmol) in 3-pyrrolidin-1-yl-propylamine (8mL). Heat the solution to 80-100 °C for 48 hours. Concentrate the mixture. Add dichloromethane (25 mL) and water (20 mL) to the residue. Separate the organic layer and wash with water (2 x 20 mL) and brine (20 mL). Dry the organic layer with sodium sulfate. Filter and concentrate to afford crude product. Chromatograph (SiO₂, 1.5-4% MeOH in CH₂Cl₂) to give the title compound 37mg (33%) as a pale yellow solid.

TLC: Rf=0.17 (silica gel, 10% CH₂Cl₂/MeOH)

MS ES⁺ m/e 491 (M+1).

By the method of EXAMPLE 101 the following compounds were prepared:

5

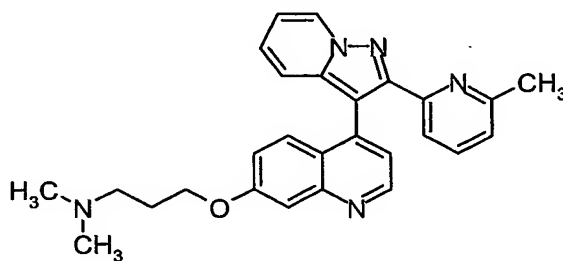
EXAMPLE #	Product (Chemical Name)	Physical Data
102	3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-propionamide	MS ES ⁺ m/e 408 (M+1).
103	3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-N-(3-pyrrolidin-1-yl-propyl)-propionamide	MS ES ⁺ m/e 479 (M+1).
104	N-(2-Dimethylamino-ethyl)-3-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-propionamide	MS ES ⁺ m/e 479 (M+1).
105	2-Pyridin-2-yl-3-quinolin-4-yl-pyrazolo[1,5-a]pyridine-5-carboxylic acid (3-dimethylamino-propyl)-amide	MS ES ⁺ m/e 450 (M+1).
106	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (2-hydroxy-ethyl)-amide	
107	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid hydrazide	MS ES ⁺ m/e 395 (M+1).
108	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (3-hydroxy-propyl)-amide	MS ES ⁺ m/e 438 (M+1).
109	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid methylamide	MS ES ⁺ m/e 394 (M+1).
110	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (3-ethoxy-propyl)-amide	MS ES ⁺ m/e 466 (M+1).
111	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (3-morpholin-4-yl-propyl)-amide	MS ES ⁺ m/e 507 (M+1).
112	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-	MS ES ⁺ m/e 488

-74-

EXAMPLE #	Product (Chemical Name)	Physical Data
	a]pyridin-3-yl]-quinoline-7-carboxylic acid (3-imidazol-1-yl-propyl)-amide	(M+1).
113	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (3-dimethylamino-propyl)-amide	MS ES ⁺ m/e 465 (M+1).
114	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid [2-(2-methoxy-phenyl)-ethyl]-amide	MS ES ⁺ m/e 514 (M+1).
115	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide	MS ES ⁺ m/e 493 (M+1).
116	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinoline-7-carboxylic acid amide	MS ES ⁺ m/e 380 (M+1).

EXAMPLE 117

Dimethyl-(3-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}-propyl)-amine



5

To a solution of 4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-ol (0.1 g, 0.28 mmol) in DMF (7 mL) add 3-dimethylaminopropyl chloride hydrochloride (0.14 g, 0.86 mmol) and cesium carbonate (0.56 g, 1.71 mmol). Stir at room temperature for 48 hour. Evaporate the DMF. Add methylene chloride. Wash with water and then brine. Dry the organic layer over anhydrous Na₂SO₄, filter the mixture, and concentrate the mixture in vacuo. Chromatograph the residue on silica gel (elute with 100% ethyl acetate, then 1% NH₄OH/5% methanol/94% methylene chloride, then 10% methanol in methylene chloride) to give the title compound 63mg (52%) as an off-white solid.

10

-75-

MS APCI⁺ m/e 438 (M+1).

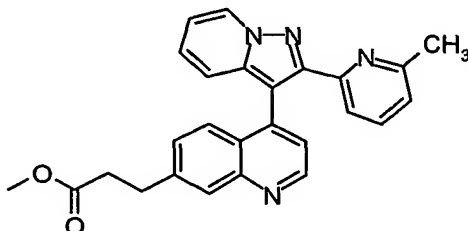
By the method of EXAMPLE 117 the following compounds were prepared:

EXAMPLE #	Product (Chemical Name)	Physical Data
118	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(2-morpholin-4-yl-ethoxy)-quinoline	MS APCI ⁺ m/e 466 (M+1).
119	Diisopropyl-(2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}-ethyl)-amine	MS APCI ⁺ m/e 480 (M+1).
120	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(2-pyrrol-1-yl-ethoxy)-quinoline	MS APCI ⁺ m/e 446 (M+1).
121	Dimethyl-(1-methyl-2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}-ethyl)-amine	MS APCI ⁺ m/e 438 (M+1).
122	Methyl-(3-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}-propyl)-amine	MS APCI ⁺ m/e 424 (M+1).
123	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(2-piperidin-1-yl-ethoxy)-quinoline	MS APCI ⁺ m/e 464 (M+1).
124	Diethyl-(2-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yloxy}-ethyl)-amine	MS APCI ⁺ m/e 452 (M+1).
125	Dimethyl-{3-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-propyl}-amine	MS APCI ⁺ m/e 424 (M+1).
126	7-(2-Morpholin-4-yl-ethoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	MS ES ⁺ m/e 452 (M+1).
127	Diisopropyl-{2-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-ethyl}-amine	MS ES ⁺ m/e 466 (M+1).
128	4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-7-(3-morpholin-4-yl-propoxy)-quinoline	MS ES ⁺ m/e 480 (M+1).
129	1-(3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridine-3-yl]-quinolin-7-yloxy}-propyl)-1,3-dihydro-benzoimidazol-2-one	MS APCI ⁺ m/e 527 (M+1).

-76-

EXAMPLE 130

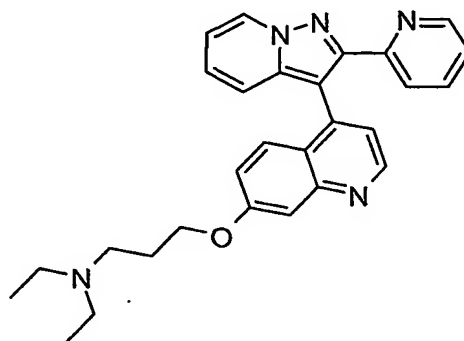
3-{4-[2-(6-Methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-propionic acid methyl ester



- 5 Add Pd/C (10%, 0.46 g) to a solution of 3-{4-[2-(6-methyl-pyridin-2-yl)-pyrazolo[1,5-a]pyridin-3-yl]-quinolin-7-yl}-acrylic acid methyl ester (0.462 g, 1.1 mmol) in MeOH (10 mL) and dichloromethane (10 mL). Bubble nitrogen for 15 minutes. Connect the hydrogen balloon to the reaction flask and stir overnight. Filter through celite and wash the celite pad with dichloromethane (50 mL). Remove the solvent.
- 10 Chromatograph the residue (elute with 2% MeOH in dichloromethane) to give the desired product as a pale yellow solid 0.27 g (59%).
- $^1\text{H NMR}$ (CDCl_3) δ 9.22-9.14 (m, 1H), 8.69-8.61 (m, 1H), 8.37-8.30 (m, 1H), 7.84-7.74 (m, 2H), 7.73-7.65 (m, 1H), 7.63-7.54 (m, 1H), 7.47-7.37 (m, 1H), 7.35-7.29 (m, 2H), 7.08-6.98 (m, 2H), 3.68 (s, 3H), 3.25-3.16 (m, 2H), 2.82-2.71 (m, 2H), 2.03 (s, 3H).
- 15 TLC: R_f =0.4 (silica gel, 10% $\text{CH}_2\text{Cl}_2/\text{MeOH}$)
- MS ES^+ m/e 423 (M+1).

EXAMPLE 131

Diethyl- {3-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-propyl}-
amine



- 5 A solution of 7-(3-chloro-propoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline (0.1 g, 0.24 mmol) in DMF was treated with N,N-diethylamine (excess) and KI (catalytic). The reaction was heated to 60°C in a sealed tube and stirred overnight. The reaction was quenched with water and extracted with CH₂Cl₂. The organic was dried and the solvent removed. The crude was purified by silica gel column to afford the
10 desired product. MS ES⁺ m/e 452 (M+1).

By the method of EXAMPLE 131 the following compounds were prepared:

EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
132	Ethyl- methyl- {3- [4-(2- pyridin-2- yl- pyrazolo[1,5- a]pyridin- 3-yl)- quinolin-7- yloxy]- propyl}- amine	7-(3-Chloro- propoxy)-4-(2- pyridin-2-yl- pyrazolo[1,5- a]pyridin-3-yl)- quinoline	N-Ethyl-N- methylamine	MS ES ⁺ m/e 438.1 (M+1).	
133	4-(2- Pyridin-2- yl- pyrazolo[1,5	7-(3-Chloro- propoxy)-4-(2- pyridin-2-yl- pyrazolo[1,5-	Pyrrolidine	MS ES ⁺ m/e 450.1 (M+1).	

EX #	Product (Chemical Name)	Starting Material A	Starting Material B	Physical Data	Comments
	-a]pyridin-3-yl)-7-(3-pyrrolidin-1-yl-propoxy)-quinoline	a]pyridin-3-yl)-quinoline			
134	7-(3-Piperidin-1-yl-propoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	7-(3-Chloro-propoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	Piperidine	MS ES ⁺ m/e 464.1 (M+1).	
135	Diethyl-{2-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-ethyl}-amine	7-(2-Chloro-ethoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	N,N-Diethylamine	MS ES ⁺ m/e 438.0 (M+1).	
136	Dimethyl-{2-[4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinolin-7-yloxy]-ethyl}-amine	7-(2-Chloro-ethoxy)-4-(2-pyridin-2-yl-pyrazolo[1,5-a]pyridin-3-yl)-quinoline	N,N-Dimethylamine	MS ES ⁺ m/e 410.2 (M+1).	

-79-

TGF- β RECEPTOR I AND II PURIFICATION AND IN VITRO KINASE
REACTIONS

For TGF- β Type I (RIT204D) and Type II (RII WT) Receptor Kinases:

5 The 6X-HIS tagged cytoplasmic kinase domain of each receptor was expressed and purified from Sf9 insect cell lysates as briefly described below:

Cell pellets after 48-72 hrs of infection were lysed in lysis buffer (LB: 50 mM Tris pH 7.5, 150 mM NaCl, 50 mM NaF, 0.5% NP40 with freshly added 20 mM β -mercaptoethanol, 10 mM imidazole, 1 mM PMSF, 1X EDTA-free Complete Protease
10 Inhibitor(Boehringer Mannheim).

Cell lysates were clarified by centrifugation and 0.45 μ M filtered prior to purification by Ni/NTA affinity chromatography (Qiagen).

Chromatography Protocol:

15 Equilibrate with 10 CV of LB, load sample, wash with 10 CV RIPA buffer (50 mM Tris pH 7.5, 150 mM NaCl, 1% NP40, 1mM EDTA, 0.25% sodium deoxycholate, added fresh 20 mM β -mercaptoethanol, 1 mM PMSF), wash with 10 CV LB, wash with 10 CV 1X KB (50 mM Tris pH 7.5, 150 mM NaCl, 4 mM $MgCl_2$, 1 mM NaF, 2 mM β -mercaptoethanol), elute with a linear gradient of 1X KB containing 200 mM Imidazole.

20 Both enzymes were approximately 90% pure and had autophosphorylation activity.

Reactions: 170-200 nM enzyme in 1X KB, compound dilution series in 1X KB/16% DMSO (20 μ M to 1 nM final concentration with 4% DMSO final concentration), reactions started by adding ATP mix (4 μ M ATP/1 μ Ci ^{33}P - γ -ATP final
25 concentrations) in 1X KB.

Reactions were incubated at 30 $^{\circ}C$ for 1 hr RIT204D or 40 min for RII WT. Reactions were stopped and quantitated using standard TCA/BSA precipitation onto Millipore FB glass fiber filter plates and by liquid scintillation counting on a MicroBeta JET.

-80-

TGF- β RECEPTOR I

All exemplified compounds were tested essentially as described above and were found to inhibit the TGF-beta Type I Receptor Kinase with an IC₅₀ of at least 10 uM. As representative of the series, Examples 43, 47, 53, and 56, inhibited the TGF-beta Type I
5 kinase with IC₅₀'s, of 0.152uM, 0.175uM, 0.806 uM, and 0.102 uM, respectively.

TGF- β RECEPTOR II

As above, all exemplified compounds were found to inhibit the TGF-beta Type II Receptor Kinase with an IC₅₀ of at least 20 uM. As representative of the series,
10 Examples 43, 47, 53 and 56 inhibited the TGF-beta Type II kinase with IC₅₀'s of 3.17 uM, 5.10 uM, 20 uM, and 0.377 uM, respectively.

p38 α IN VITRO KINASE ASSAY

Active p38 α /SAPK2 α was purchased from Upstate Biotechnology (cat#14-251).
15 A known p38 α substrate from EGFR was used in the assay (Young, et al. (1997) JBC 272: 12116-12121).

Reactions were performed in 1X kinase buffer (25 mM Tris-HCl pH 7.5, 5 mM β -glycerophosphate, 2 mM DTT, 0.1 mM Na₃VO₄, 10 mM MgCl₂, 1 uM Microcystin) with 5 nM p38 α , 62.5 uM substrate, 40 uM to 0.2 nM compound dilution series in 1X
20 KB/16% DMSO (final 4% DMSO concentration). Reactions were started by addition of 100 uM ATP (final concentration) with 1 uCi ³³P- γ -ATP in 1X KB and incubated at 30°C for 40 min. Reactions were stopped with H₃PO₄ and quantitated on Millipore PH phosphocellulose filter plates by liquid scintillation counting on a MicroBeta JET.

Representative data for compounds of the current invention with the p38 α IC₅₀
25 <20.00 (uM): Examples 45, 46, 78 and 117 gave, respectively, IC₅₀'s of 0.390, 0.369, 0.233 and 0.078 uM.

MV1LU p3TP-LUX ASSAY

A stable Mv1Lu clone (C1) containing the p3TP-Lux reporter was created by
30 standard transfection and puromycin selection protocols. This stable clone was used to

-81-

screen the example compounds for their ability to inhibit TGF- β dependent luciferase production as briefly described below:

1. Plated Mv1Lu C1 cells in Wallac™ Black Isoplates.
2. Allowed cells to adhere overnight.
- 5 3. Removed media and replaced with 0.5% FBS DMEM media.
4. Added the compound dilution series in 0.5% FBS/DMEM containing 1% DMSO such that the final compound concentration ranged from 20 μ M to 0.1 nM and the final DMSO concentration was 0.2%.
- 10 5. Incubated at 37°C/5% CO₂ for 2 hrs.
6. Added 0.5% FBS/DMEM as control or TGF- β 1 diluted.
in 0.5% FBS/DMEM (final concentration of 10 pM) to the +/- TGF- β wells respectively.
7. Incubated for 16-20 hrs. at 37°C/5% CO₂.
- 15 8. Removed media and rinsed 1X with PBS.
9. Removed PBS and lysed the cells with 1X Passive.
Lysis Buffer (Promega) at room temperature.
10. Counted relative luciferase activity on the MicroBeta JET by injecting Luciferase Assay Reagent II (PROMEGA).
- 20 The use of the above assay in measuring TGF- β responsive activity is described in Wrana, et al. Cell 71: 1003-1014 (1992).

As above, all exemplified compounds were found to inhibit TGF-beta dependent luciferase production with an IC₅₀ of at least 20 μ M. As representative of the series,
25 Examples 43, 47, 53 and 56 inhibited luciferase production with IC₅₀'s of 0.120 μ M, 0.100 μ M, 0.487 μ M, and 0.135 μ M, respectively.

PHARMACEUTICAL COMPOSITIONS

The compositions of the present invention are therapeutically effective TGF- β inhibitors, noted above. The composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered transdermally and maybe formulated as sustained relief dosage forms and the like.

The method of treating a human patient according to the present invention includes administration of the TGF- β kinase inhibitors. The TGF- β kinase inhibitors are formulated into formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) the compounds. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The formulations useful for separate administration of the TGF- β inhibitors will normally consist of at least one compound selected from the compounds specified herein mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable

container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therapeutic substance. Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention are capsules, tablets, suppositories, injectable solutions, creams and ointments. Especially preferred are formulations for inhalation application, such as an aerosol, for injection, and for oral ingestion.